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CULTURAL VARIATION AND THE PRACTICAL PEDIATRICIAN

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THE term "culture" is frequently used in a somewhat narrow sense to apply more or less exclusively to the artistic, academic, and spiritual activities of a community. However, the social anthropologist considers it too restricting to equate culture only with such important phenomena as architecture, literature, and philosophy—a wider definition is required, for "Culture covers not only the arts, sciences, religions and philosophies to which the word is historically applied, but also the system of technology, the political practices, the small intimate habits of daily life, such as the way of preparing or eating food, or of hushing a child to sleep."[1] Similarly, Foster[2] employs the following definition: "the common way of life shared by the members of a group, consisting of the totality of their tools, techniques, social institutions, behavior patterns, attitudes, beliefs, motivations, systems of values and the like."

CULTURAL VARIATION

Culture patterns vary all over the world and, although ideally a knowledge of all interrelated aspects of the particular culture would be of great benefit to the practical pediatrician, certain facets are of especial significance, particularly customs relating to pregnancy and childbirth, methods employed in child rearing, local food ideology, and indigenous medical beliefs.

Unprejudiced analysis, based on dispassionate and unbiased scientific observation clearly shows that both rational and irrational attitudes, and beneficial and injurious customs, are to be found in every part of the world, whether in Boston, Manchester, or Southeast Asia. The following examples may, for instance, be quoted as sometimes being of importance to a greater or lesser extent in the field of child health among different socio-economic groups in Britain—the prevalence of totally unnecessary "social" circumcision, overrigid attitudes toward toilet training and breast feed-

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ing, the use of proprietary "gripe-water" types of medicines and potentially dangerous mercurial teething powders, the belief that fish is a specific "brain food" for infants, and such superstitions as the belief that a baby boy born in a caul is lucky and, in particular, will not be drowned. From the general nutritional point of view, it is worth noting that the universal prejudice in Britain against protein-rich frogs, snails, dogs, and insects is so great that, even during the period of maximal food shortage during the last war, no suggestion was made that these might be employed for the supplementary feeding of children, despite the fact that these items form customary, much relished and nutritious foods in other parts of the world.

IMPORTANCE TO THE PEDIATRICIAN

If it is agreed that culture patterns, including the food habits and the practices associated with pregnancy and methods of child rearing, vary greatly in different parts of India, it becomes necessary to consider in what practical ways a knowledge of these beliefs and attitudes is important to the scientific pediatrician.

A description of what appears to be the present logical trend in pediatrics will show the main value of this approach. It has become apparent to the thinking pediatrician that an exclusively curative approach to child health is illogical, shortsighted, and overexpensive. It is, for example, unsatisfactory to treat children with ascariasis and Guinea worm infection, with malaria and malnutrition, if, at the same time, no effort is made to prevent the almost inevitable recurrence of these conditions when children leave the artificial surroundings of the hospital ward and return to their home environments. As a result of this mental evolution, the curative-preventive pediatrician has developed, with an appreciation of the importance of both overlapping and interdependent aspects of child health.

A consideration of the ways in which child health may be protected and improved suggests three main preventive approaches: (1) public health measures, such as an improved water supply, residual spraying with DDT, and immunization programs; (2) general socioeconomic measures, including increased employment and a higher standard of living, and the spread of adult education; and (3) health education. Important as are the first two of these, it is usually in the last—the field of health education—that the practical pediatrician has most chance to contribute personally, by means, for example, of counseling on infant feeding, given in the welfare clinic, or advice to parents when their children are discharged from hospital.

Although to the uninitiated, the art of health education in this or any other context may appear to be a straightforward matter, easily accomplished by a display of logic and a marshalling of posters, experience has unfortunately shown this not to be the case, especially among peasant peoples in nonindustrialized tropical countries. The resistance, or lack of response, to standard health education measures so often found, is related to the fact that attempts at altering people's habits, ways of life, and customary behavior are never made *in vacuo*, but in competition with, and against the resistance of, deep-rooted and time-hallowed indigenous beliefs. Foster[3] expresses this view when he says: "The public health specialist is not working in a

vacuum—rather he is working in an area in which the subject already has definite and hard-to-shake beliefs, which they are just as sure are correct as he is sure they are mistaken."

In brief, then, it has become clear—largely as a result of the work of Foster and his colleagues—that, in any health field, it is usually necessary to know a group's present attitudes and beliefs in order to modify them successfully by means of health education, and this applies perhaps with especial force to the field of child health. New knowledge will be accepted only in so far as it can be made to fit into the general pattern of custom and belief of the people.[2, 3, 4]

Second, from the point of view of scientific medicine, it has become increasingly realized that detailed investigation of methods used in child rearing among different cultural groups may often help to contribute to world knowledge of child care. For example, the rigid "by-the-clock" system of breast feeding has now been largely abandoned in Western countries in favor of the so-called "self-demand" method, partly as a result of observation of more natural methods employed in other parts of the world. This cross-cultural type of approach promises, for example, to be particularly rewarding in improving our understanding of the effect of child training on personality development.[5]

Finally, but certainly not least in importance, it seems probable that the pediatrician will be able to establish a better rapport with the families with which he is concerned, whether in the welfare clinic or as outpatients, and more easily earn their confidence, if he understands, appreciates, and learns to think in terms of their beliefs and attitudes.

INVESTIGATION OF CULTURAL VARIATION

The correct approach to cultural variation may perhaps be illustrated best by assuming that the pediatrician finds himself in a part of the world which is for him *terra incognita*—as, for example, if an Indian pediatrician

Fig. 1.—Early practical mothercraft. Dyak girl in Sarawak carrying and tending younger sibling.

were to set up a child welfare clinic in the center of Brazil. Under this type of circumstance, it would seem wise to conduct a preliminary investigation somewhat along the following lines: (1) investigate, so far as possible, relevant indigenous methods and practices; (2) make an *unprejudiced* analysis of these, based on scientific principles, but bearing in mind the

local background (i.e., climatic, geographic, economic, agricultural, etc.); (3) divide the practices encountered into three groups—the beneficial, which should be encouraged, the harmless or neutral, which need not be interfered with, and the harmful, which should be overcome, if possible, by persuasion and demonstration, or integrated in some "neutralized" form, as will be described later.

Fig. 2.—Scene in "joint family" house in lower socioeconomic group in North India, demonstrating intimate relationships possibly resulting in quite different psychological attitudes and problems in children compared with those found in Western single-unit families.

CORRECT AND INCORRECT ATTITUDES

From a practical point of view, various attitudes may be adopted by the scientific pediatrician with regard to indigenous customs, and these may be considered as falling into two groups—the incorrect and the correct.

Incorrect Attitudes.—

Lack of awareness: With a foreigner, working outside his own country, and sometimes even with a national pediatrician, who is often town-bred and from the upper socioeconomic group, there may be a considerable lack of awareness of the complexity of the indigenous beliefs and customs existing in the village. The fault here would appear to be mainly educational, as the pediatrician has usually not had his mind orientated during his training toward considering or investigating his patients' socioanthropological backgrounds.

Refusal to recognize: In some cases the pediatrician may be aware, to a varying extent, of local views and practices, but, often unconsciously, may adopt an attitude whereby he ignores them. In other words, he may compartmentalize his mind, so that in the clinic he deals only in terms of scientific pediatrics as laid down in the standard textbook, which is, anyway, usually written with a Western cultural background assumed.

Derision: Sometimes, unfortunately, the pediatrician may adopt an attitude of quite unwarranted superiority and look down on, or even deride, local village customs and traditional practices. This view that the methods of the villager are merely the inferior ways of an illiterate, ignorant peasantry is absolutely unwarranted—in many cases apparently strange practices may, in fact, represent time-tested and wise adjustments to a harsh and hostile environment.

Correct Attitudes.—

Primarily, then, it is necessary for the pediatrician to be aware of and sympathetic toward local views, attitudes, and customs. Depending upon whether they are considered scientifically desirable or not, so one of the following lines of approach may be used:

Adoption: If a custom or practice appears to be beneficial in the particular local background, then it should be encouraged and adopted into the pediatrician's health teaching. For example, breast feeding prolonged into the second year of life may be judged biologically necessary for the growth and survival of infants in many subtropical and tropical communities, especially, for example, in the tsetse fly belt of equatorial Africa, where cattle cannot be raised. Under these circumstances, the pediatrician will have to reorientate his ideas and methods.[6]

Fig. 3.—Successful and effortless prolonged breast-feeding African mother in North Kenya.

Persuasion: Numerous indigenous practices may be found to be absolutely undesirable when judged by scientific criteria—as, for example, the use of cow dung as a dressing on the umbilicus of the newborn child, or the failure to introduce supplementary foods to an infant until he can walk. Under these circumstances, the correct

Fig. 4.—Attitude to disease. Yemenite child with multiple abdominal scarification marks made to let out evil spirits.

approach for the pediatrician is undoubtedly to attempt to alter the parents' belief in the particular custom by means of persuasion, strengthened, wherever possible, by convincing, practical demonstration of the superiority of his methods. This may be extremely difficult, or even impossible, especially with an essentially pragmatic peasant population, when dealing with such long-term aspects of child health as the nutritional benefits of different methods of infant feeding. It is usually easier to convince when the results are rapidly and easily demonstrated, as, for example, the superiority of benzyl benzoate emulsion over herbal preparations in the treatment of scabies, or the efficacy of penicillin therapy in yaws.

In any case, in order to use persuasion to best advantage, the pediatrician must fully understand the resistances that are likely to arise against his advice, and this he can do best by being conversant with the local culture pattern.

Integration: Sometimes customs and attitudes considered undesirable by the scientific pediatrician may be rendered harmless by modification and integration. Thus, if orange and other fruit juices are classified as "cold" (*tonda*) in a particular food ideology and because of this cannot be given during the winter months, it would seem legitimate to make use of the culturally acceptable and scientifically harmless technique of neutralizing the essential inherent "coldness" of the juice by adding a little honey, which is "hot" (*garam*), if by this means the mother will be more willing to allow the infant to take the ascorbic acid-containing juice.

Similarly, sometimes by retaining and integrating, or at least not opposing, a particular custom, which to the scientific viewpoint may seem quite immaterial to the child's health, it may be possible to keep or increase the parents' confidence. In this avoidance of unnecessary conflict, major difficulties may be circumvented by carefully "charting a course along the reefs of culture, instead of crashing precipitously upon them."[7]

For example, in many parts of the world, the exact method of disposal of the placenta is felt to be of real moment. In these circumstances, allowing a relative to remove the placenta for burial, or whatever other method is employed, may encourage mothers needing special obstetrical care to come into the maternity hospital and so lessen the risk of birth trauma, a major pediatric concern.

In the same way, a knowledge of and, so far as possible, a respect for such conceptions as especially suitable days for medical procedures, such as vaccination, or of culturally defined efficacious times of day for taking medicines, should be cultivated. These practices can often be quietly adhered to—and may ensure that the patient will receive the main essentials of a particular form of therapy more willingly.

It may be argued that by adopting this type of method, the pediatrician is helping to perpetuate what are, when judged by present scientific knowledge, irrational beliefs. If alteration of ideas by persuasion were an easy matter, this sort of approach would certainly be unnecessary. Unfortunately this is definitely not the case, so that some type of integration may have to be employed as an interim measure until the spread of education causes many of these irrational attitudes to disappear. It is not suggested, however, that the health worker should give his advice using, for example, the terms and reasoning of the local food ideology, but rather that he should work within this framework, making use of it without supporting it. In the instance already cited, the pediatrician, knowing the customs and attitudes of the particular group, would advise the use of fruit juice with a little added honey, without either mentioning or condoning the "hot-cold" food classification, which he knows to be the basis of the difficulty.

The correct attitude toward any particular custom—whether for example, to attempt to persuade or to integrate temporarily—will have to be decided by the health worker. There is no absolute rule, and a decision will depend upon such factors as the pediatrician's estimate of local attitudes and resistances, and on the amount of time available in the clinic.

CHILD WELFARE CLINIC IN WEST BENGAL

The following examples, based on personal experience in a rural child welfare clinic in West Bengal, will illustrate a practical application of the type of approach outlined in the present paper. In almost all instances, mothers bringing their children to the clinic were illiterate Bengali villagers of the lower socioeconomic group and of the Hindu religion.

Foods and Illness.—Apart from the fundamental Hindu division of foods into *amish* (nonvegetarian) and *niramish* (vegetarian) the dominant food ideology among the village mothers attending the clinic was found to be the "hot-cold" (*garam-tonda*) classification, based upon supposed inherent properties of foodstuffs.* According to this view, eggs, meat, milk, *musuri dhal* (*Lens esculenta*), honey, sugar, and cod-liver oil are regarded as being to varying degrees *garam;* while lemon,

*A similar classification of disease and diet (*caliente-frio*) is also prevalent among some Latin American peasant groups.[3] This appears to stem ultimately from the humoral pathology of Hippocrates and Galen, which reached medieval Europe via the Arab world and was transmitted to Hispanic America by the conquistadors. As this concept appears to be an ancient one in India, stemming back to early Sanskrit Ayurvedic literature, it is possible that it may have originated in India and spread to influence and mold early Greek thought in this respect.

orange, rice, water, acid buttermilk (*lassi*) and curd (*dahi* or Indian yoghourt) are classified as *tonda*.

Apart from difficulties in infant feeding that may arise as a result of a reluctance to give such *garam* items as eggs and cod-liver oil during the warm weather, of greater importance is the fact that illnesses are also classified as being *garam* or *tonda*, and that "hot" or "cold" foods cannot be given during like illnesses.

Bronchitis.—For example, an upper respiratory tract infection, such as bronchitis, is regarded as a "cold" or *tonda* malady. Scientifically, in this type of case it may be desirable to advise the mother to give sulfonamides, together with plenty of water to drink and the lighter portion of the normal diet, including rice preparations. This, however, would not be considered as satisfactory by the mother, as both water and rice are classified as *tonda* and, therefore, to be avoided in this type of illness.

In this instance persuasion may be possible but often may not be successful against such a deeply ingrained food belief, and, in this case, the two attitudes—that of the pediatrician and that of the mother—can be successfully integrated by advising the mother to give sulfonamides, together with water flavored with honey and rice cooked in milk. The mother will accept this advice much more readily, as the honey and the milk are thought to neutralize the "cold" in the water and in the rice, and scientifically the same end point has been reached.

Diarrhea.—In children recovering from diarrhea, mothers are frequently reluctant to introduce milk, even if diluted, as both the food and the illness are classified as *garam*, so much so that continued feeding with carbohydrate gruels may, in this type of case, act as the starting point for the subsequent development of the protein deficiency syndrome known as kwashiorkor.

Frequently, in this sort of situation it is desirable, from a scientific point of view, that the child should be given a bland, easily absorbable, low residue carbohydrate gruel, a water-absorbing, pectin-containing food, and dilute milk. In a West Bengal rural child welfare clinic, it appears that this is best achieved by adopting three local dietary remedies, which appear to coincide exactly with the scientific viewpoint. By using the carbohydrate *chira mondu* (hand-mashed flat rice) and, as the pectin food, a sherbet made of the Indian wood apple (*Aegle marmelos*), one is employing traditional dietetic treatment while, in dilute *lassi* (acid buttermilk), one has an acceptable and familiar remedy. The buttermilk, being both acidified and defatted, and a *tonda* food, is particularly suitable from all points of view.

Vaccination.—As in certain other parts of the world, smallpox, partly perhaps because of its striking and characteristic appearance and its high mortality, is often regarded by villagers in West Bengal as due to divine visitation of the goddess *Shitala*, and, because of this, some years back, in the early days of the health center, vaccination was actively refused. At the present time, however, a great change has come about, so that vaccination is nowadays welcomed and even sought after by village mothers. This is, of course, an excellent example of successful health education by persuasion and demonstration, as mothers have

themselves come to observe that, if their children are vaccinated, they are no longer liable to be blinded, disfigured, or killed by smallpox.

Childbirth and the Maternity Home.—All over the world, the life crisis of childbirth is associated with special customs, *rites de passage*, and precautionary practices. This is equally true in rural West Bengal and it is of interest to see how these can be dovetailed and integrated into the otherwise alien background of the small maternity hospital attached to the rural center.

As no particular beliefs appear to be held concerning the length at which the cord should be cut, as in some countries, no difficulty arises here. With regard to the placenta, in the traditional home delivery this is buried by the *dai* (hereditary indigenous midwife). However, the exact details of this practice do not appear to be very important in this locality, so that mothers seem to be quite content for the placenta to be disposed of by the maternity home staff in a deeply dug rubbish pit. The ritual seclusion universally practiced by Hindu mothers after birth can be adhered to, at least functionally, by visitors' not approaching nearer than a few feet from the bed, and by the food's being brought from home by relatives and emptied into the mother's plate, which she leaves just outside the ward. In this case, care is taken not to touch the mother's plate with the food container during the process of pouring.

Attitudes toward the disposal of the shriveled umbilical stump vary. Many mothers do not seem to mind if this is thrown away, although some are in the habit of using it in a *maduli* (protective charm) worn round the baby's neck. In the latter case, the maternity home staff raise no objection.

Various ceremonies are performed in the neonatal period. One of these, *jata karman*, can be and is carried out in substance by the mother herself, putting a drop of honey on the neonate's tongue. Similarly, on the sixth evening, the mother will be anxious to be home for the night vigil kept during *Shosti puja* (dedication of the baby to *Shosti*, the goddess of children). However, if the mother has to stay in the maternity home longer

Fig. 5.—Toddler in rural West Bengal, showing various types of preventive medicine: (1) vaccination scar visible on left arm; (2) *maduli* (charm) around neck, iron bangle on left wrist, and beads around groin as protection against evil spirits; (3) *Kajal* (carbon and oil) outlining eyes as beautifier and to ward off "evil eye" (*nazar*).

than this, a satisfactory compromise can be achieved by the relatives' doing a part of the ceremony in the home, while the rest can be completed by the mother on the twenty-first day, when she has returned home. There are, however, two days on which the mother is very anxious to be home—the first is on the eighth day, for the ceremony of *atkore-batkore*, and the second on the tenth day, when the ritual purificatory bath is taken. Knowing this, the maternity home staff will make every effort to see that the mother leaves the hospital in time.

It can be seen, then, that, owing to the sensibly flexible attitude of the staff, an excellent working arrangement has been built up whereby the practices and beliefs of the mothers have been suitably integrated into the background of a modern maternity home.

Mixed Diet in Infant Feeding.—As in many parts of India, in rural West Bengal one of the ancient Hindu rites which is always observed is *annaprasan* (rice-feeding ceremony), which is here performed at 6 months of age for a boy and at 7 months for a girl.

It would seem likely that the original purpose of this custom was both to celebrate the baby's having survived the dangerous first half year of independent existence, and, at the same time, to commence widening the infant's diet. Investigation shows, however, that a not inconsiderable percentage of present-day villagers perform the ceremony punctiliously, but do not continue with rice and other foods thereafter, sometimes not introducing them until the child can walk or has teeth in both upper and lower jaws.

Nutritionally it is, of course, necessary for the infant to have foods other than milk, at least from about the end of the first six months onward, and it would seem profitable to use a reference to this wise and ancient practice as a practical lever in health education to persuade village mothers of the need for foods other than milk after the age of 6 months.

CONCLUSION

To understand fully the motivations behind the customs and beliefs of a particular people needs the skill of a trained socioanthropologist, who not only knows the language but has been able to live with the particular group unobtrusively and on equal terms. The assistance of such a person should always be sought—if possible in person, if not, in the available literature. Usually, however, the pediatrician working in a technically developing tropical region will himself have to attempt, somewhat amateurishly, to piece together at least the more relevant features of the particular culture pattern, especially the customs affecting children and pregnant women. He will then find himself better able to understand his patients' problems and to gain the parents' confidence more fully. In addition, he will be able to plan out and put into effect scientifically based preventive and curative measures in ways that are interwoven into the local pattern of beliefs and, therefore, the more likely to succeed.

From a wider perspective, it is highly desirable that world-wide investigation should continue into cultural variation and its effects on child health and development. Scientific medicine, of which pediatrics is one

important discipline, has its ultimate historical roots in knowledge from all over the world. The next phase may well be the further incorporation and fusion of the valuable and worth while from all cultural groups into an enriched, expanded, and truly global system of child care.

Figs. 1 through 4 are used with the kind permission of the World Health Organization, Geneva, Switzerland.

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How to Handle a Fretful Infant

A peevish and fretful disposition in infancy, if not, as is generally the case, the result of errors in nursing, or too close confinement in a stagnant and impure atmosphere—by which the energies of the system are impaired—digestion materially impeded, and the sentient organs subjected to impressions, if not positively painful, at least uncomfortable—is often induced by unkindness, impatience, or want of temper on the part of the mother or nurse. An infant whose natural inclinations are continually thwarted—who is placed in the cradle and attempted to be forced to sleep, when it would be awake and playful—and whose disinclination to repose, and the cries by which this is expressed, expose it to angry chidings—a passionate slap, or a rough shaking from its attendant—or whose calls for its natural food, or to be nursed or diverted, are repelled by equally injudicious means, will seldom fail to become peevish, restless, and fretful. It may be proper, on many occasions, to soothe an infant to repose by gentle fondling and the soft lulling notes of some nursery air; but if these do not quickly succeed in producing the desired effect, it is better to desist at once, than to resort to any others.

D. Francis Condie, on the Diseases of Children, 1871.

STUDIES ON PANCREATIC ENZYMES

A Comparison of Fasting Duodenal Juice Before and After Gastric Aspiration

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THE importance of the analysis of duodenal juice for enzymatic activity of the pancreatic enzymes has been fully established. The most valuable application of this analysis is the diagnosis of cystic fibrosis of the pancreas, and the absence of the three pancreatic enzymes, trypsin, amylase, and lipase, is accepted as almost conclusive proof of the disease.[1-6]

Whether on not there are patients with symptoms of the celiac syndrome who have a deficiency of just a single pancreatic enzyme has not been proved. However, Andersen[7] has reported patients with the characteristic clinical picture of idiopathic celiac disease who had laboratory evidence of starch intolerance, and in some of these she was able to demonstrate a deficiency of pancreatic amylase alone.

A fasting duodenal specimen may be composed of bile, pancreatic juice, and some of the gastric contents. The latter may contain saliva with its salivary amylase, and whether or not this enzyme can materially affect the result of the analysis of duodenal contents for pancreatic amylase activity has not been fully investigated. The routine method of obtaining duodenal juice for analysis does not necessarily prevent gastric juice and swallowed saliva from entering the duodenum during the procedure.

Patients on whom a diagnostic duodenal intubation is performed may not be in an ideal state of hydration and electrolyte balance, especially during hot weather. Removal of a large amount of gastric and salivary secretion can increase the depletion of electrolytes. Therefore, a duodenal intubation should be accomplished in as short a period of time as possible. Removal of gastric content should be avoided unless it is necessary to exclude it from the duodenum in order to obtain a satisfactory sample of pancreatic juice. For this reason, it would seem important to know if the routine method of collecting duodenal samples for enzymatic analysis is satisfactory in the study of patients with the celiac syndrome. A study of this problem was made and this paper is a report of the enzymatic analysis of fasting duodenal juice before and after gastric aspiration in sixty-three patients from 1 month to 11 years of age, for a diagnostic duodenal intubation.

PROCEDURE

Nothing but water was allowed after mindnight on the morning of the study. The intubation was started

From the Children's Hospital of Philadelphia, and the Department of Pediatrics, School of Medicine, University of Pennsylvania.

about 7:30 A.M., and was always carried out in the fluoroscopic room. The patients were restrained when necessary, and an attendant was always present. No sedation was used. Two types of tubes were used in the study. In the first forty patients a plain tip Levin tube, size 12, was tied with black silk to a size 12 Miller-Abbott tube from which the balloon was removed. The two tubes were tied together in such a relation that when the distal Miller-Abbott tube was in an ideal position in the duodenum the Levin tube would be in the stomach for aspiration of gastric contents. In the remaining twenty-three patients, a single Miller-Abbott tube, size 12, similar in its basic construction to that used by Gibbs[8] for simultaneous aspiration of gastric juice and duodenal juice, was employed. The balloon was removed from the lower end of the tube and a small silver tip substituted. A set of four openings one-half inch apart was made into the lumen of the tube for duodenal drainage, and another set of six openings one-half inch apart was made in the other lumen for gastric drainage.

The oral route for passage of the tubes was preferred since it was less painful and allowed more manipulation of tubes than the nassal route. When the distal tip of the duodenal tube was in or near the pyloric antrum, as determined by the fluoroscope, the tube was slowly pushed forward in an effort to force it through the pylorus. In no case was the tube simply left in good position in the stomach for gastric peristalsis to carry it through the pylorus. With experience it was found that the tube could be pushed into the duodenum in nearly every instance, which represents a definite improvement over the technique of simply relying on gastric peristalsis to carry the tube into the duodenum, as was done in a previous study.[9]

After the tube was shown by fluoroscopic examination to be in the desired position, gentle aspiration of duodenal juice with a 10 ml. syringe was begun. When the juice obtained was bile-colored and strongly alkaline to nitrazine paper, collection of the first sample of 3 ml. was begun. Frequent checking with the nitrazine paper was continued throughout the collection of the sample of juice. Although multiple samples of duodenal juice were not collected for analysis in this study, care was taken to discard any material from the duodenum that was not characteristically yellow in color and strongly alkaline in reaction. Then the stomach was gently, but as thoroughly as possible aspirated with a 10 ml. syringe, and was kept as empty as possible during the collection of a second 3 ml. specimen of duodenal contents via a fresh syringe. The first milliliter of juice obtained at the beginning of the second collection was discarded, since it might represent duodenal contents mixed with gastric contents. Both test tubes containing the duodenal samples were kept in ice until analyzed later in the morning. The complete duodenal intubation procedure required on an average of two hours. No record was kept of the amount of gastric juice or saliva, and no determination of gastric acidity or blood electrolytes was made. Analysis of duodenal juice for trypsin, amylase, and lipase was done according to methods previously referred to,[9] and a pH determination was made on each speci-

TABLE I. COMPARISON OF DUODENAL JUICE BEFORE AND AFTER GASTRIC DRAINAGE

INITIALS AND AGE	FINAL DIAGNOSIS	DUODENAL SPECIMEN NO. 1 (ROUTINE FASTING)				DUODENAL SPECIMEN NO. 2 (AFTER GASTRIC ASPIRATION)			
		T*	A*	L*	pH	T*	A*	L*	pH
1. R. W. 3 yr.	Cirrhosis of the liver	32	30	3	7.7	16	23	3	7.8
2. C. S. 4 yr.	Abdominal pain of undetermined cause	64	26	6.3	7.3	64	26	6.5	7.0
3. E. C. 1 yr.	Diarrhea	64	19	11	7.2	64	17	11	7.6
4. W. D. 2 yr.	Idiopathic celiac disease	64	23	11.1	7.5	32	23	2.6	7.3
5. R. W. 10 wk.	Milk allergy	320	22.5	12.5	7.0	16	7.9	11.7	6.9
6. S. F. 1½ yr.	Idiopathic celiac disease	64	17	13.6	7.5	64	19	10	7.0
7. L. F. 8 yr.	Diarrhea	64	18	11.2	7.6	64	18	7.9	6.7
8. L. S. 3 mo.	Oxyuriasis	64	11	12.3	7.4	64	10.7	12.7	7.14
9. E. C. 6 mo.	Idiopathic celiac disease	32	18	11	7.1	32	2	11	6.6
10. R. W. 4½ yr.	Early cirrhosis	32	30	3	7.7	16	23	3	7.7
11. J. J. 1½ yr.	Tracheal cyst	32	27	7	6.5	32	27	0	7.0
12. O. L. S. 1 yr.	Malnutrition	7	29	11	8.0	7	29	17	7.5
13. A. S. 14 mo.	Feeding problem	3	15	13	8.2	64	17	17	8.0
14. B. W. 15 mo.	Diarrhea	7	21	9.5	8.0	32	11	9.6	8.1
15. J. K. 3 yr.	Idiopathic celiac disease	64	27	12.5	8.1	64	30	12.0	8.4
16. S. B. 7 mo.	No disease	32	19	8	7.4	32	19	13.0	7.0
17. R. S. 3 mo.	Malnutrition	32	9.4	2.4	7.06	16	9.4	3	7.4
18. T. M. 21 mo.	Possibly bronchiectasis	64	26	2.9	7.39	64	26	3	7.5
19. J. C. 5 mo.	Feeding problem	320	2	5.5	7.39	64	5.7	9.5	7.2
20. K. M. 3 mo.	Malnutrition	16	4.0	3	7.42	16	7	2.5	7.42
21. R. C. 2 yr.	Idiopathic celiac disease	32	22	14	7.0	32	23	0	7.0
22. R. S. 2 yr.	Diarrhea	16	29	6	7.3	32	22	4.5	7.6
23. S. W. 2 yr.	Bronchopneumonia	8	2.5	1	7.35	16	1.7	8	7.45
24. R. O. 10 mo.	Idiopathic celiac disease	16	26	10	7.7	16	27	10	7.89
25. B. F. 2½ yr.	Malnutrition	16	18.7	2.5	7.1	16	29.8	1.8	7.0
26. M. C. 1 mo.	Celiac syndrome	64	3	5.7	6.7	16	7.1	7.1	6.8
27. D. B. 11 yr.	Bronchial asthma	32	29.6	11.4	7.0	64	25	11.4	7.0
28. F. C. 3 yr.	Idiopathic celiac disease	32	28	10.2	7.4	32	27	3.8	7
29. D. H. 7 mo.	Malnutrition	32	4.1	8.1	7.3	64	4.5	9.6	7.5
30. G. F. 10 mo.	Feeding problem	32	7.0	18.2	7.0	32	12.8	18.2	7.1

*T, Trypsin; A, amylase; L, lipase.

TABLE I—CONT'D

INITIALS AND AGE	FINAL DIAGNOSIS	DUODENAL SPECIMEN NO. 1 (ROUTINE FASTING)				DUODENAL SPECIMEN NO. 2 (AFTER GASTRIC ASPIRATION)			
		T*	A*	L*	pH	T*	A*	L*	pH
31. N. P. 16 mo.	Idiopathic celiac disease	32	17.3	4.5	7.4	64	22.8	9.5	7.8
32. S. H. 7 yr., 9 mo.	Chronic tracheitis	64	7.1	11.4	6.79	64	6.1	4.9	7.21
33. J. C. 5 mo.	Congenital megacolon	32	12.3	17.6	7.91	16	3.1	25	7.49
34. R. G. 21 mo.	Asthmatic bronchitis	32	18.6	24.8	6.78	32	3.9	17.8	6.9
35. M. S. 5 mo.	Feeding problem	64	7.4	0	7.3	32	4	5.6	7.4
36. J. M. S. G. 4 mo.	Diarrhea of unknown cause	16	2	6	6.8	16	2.5	7.8	7.85
37. J. W. 8½ mo.	Malnutrition	32	28	2.8	7.6	32	28	2.5	7.8
38. A. W. 2 yr., 9 mo.	Acute ethymoiditis	64	23	4	7.08	64	0	0	7.78
39. J. A. 2 yr.	Marasmus	32	27	0	7.78	32	4.5	0	7.92
40. F. C. 11 yr.	Duodenal ulcer	32	20	11	6.58	32	22	2	8.06
41. L. F. 6 wk.	Jejunal atresia	32	3	9.5	7.08	16	0	7.5	7.53
42. G. M. 3 mo.	Diarrhea	16	1.7	30	7.1	16	1.1	5.5	7.0
43. B. H. 18 mo.	Idiopathic celiac disease	8	17.0	4.2	7.1	32	21	6.4	7.2
44. L. D. 4 mo.	Megacolon	64	8	5.3	7.35	64	2	5	7.82
45. V. F. 7 mo.	Feeding problem	32	10	5	6.38	32	10	5	6.6
46. T. W. 10 wk.	Feeding problem	32	3	13	8.05	32	3.5	9.5	7.9
47. J. S. 16 mo.	Feeding problem	64	23	12.5	7.4	64	23	16.5	7.48
48. W. R. 11 mo.	Undiagnosed	64	20	3.5	7.4	64	21	0	7.5
49. M. P. 7 mo.	Malnutrition	64	18	8.9	7.1	64	18	35	7.0
50. S. R. 7 wk.	Feeding problem	32	4	5.2	7.8	32	4	6.2	7.82
51. D. S. 2 yr.	Bronchiectasis	64	12	5.0	7.2	32	8	3.0	7.2
52. P. S. 7 mo.	Feeding problem	32	26	3.5	7.3	64	16	11	7.9
53. M. O. 2½ yr.	Eosinophilia	32	11	19.4	7.04	64	9.8	22.4	7.34
54. N. H. 4 yr.	No disease	32	20.7	12.8	7.38	12	22.1	10	7.35
55. C. H. 7 mo.	Feeding problem	16	9.7	23.2	7.2	16	3.1	2	7.3
56. T. M. 1 yr.	Diarrhea	320	22.2	29.5	8.13	640	4.5	3.65	7.5
57. C. M. 2 mo.	Feeding problem	32	9	2.7	7.0	8	8	5.0	6.7
58. D. M. 2 yr.	Feeding problem	64–	26.6	5.1	7.0	64–	22	6.1	7.6

*T, Trypsin; A, amylase; L, lipase.

TABLE I—CONT'D

INITIALS AND AGE	FINAL DIAGNOSIS	DUODENAL SPECIMEN NO. 1 (ROUTINE FASTING)				DUODENAL SPECIMEN NO. 2 (AFTER GASTRIC ASPIRATION)			
		T*	A*	L*	pH	T*	A*	L*	pH
59. C. L. 2 yr.	Malnutrition	64–	28.9	4.6	7.4	64–	31.7	11.7	7.6
60. C. H. 7 mo.	Malnutrition	64–	9.7	23.2	7.2	64–	3.1	2	7.3
61. M. G. 17 mo.	Chronic bronchitis	16	20.8	15.8	7.9	32	21.5	10.5	7.5
62. L. H. 6 mo.	Idiopathic celiac disease	64	11.2	14.9	6.8	64	11	20.3	7.8
63. E. G. 2 yr.	Diarrhea	64	9.9	16.9	7.0	64	10.9	10.9	7.1

*T, Trypsin; A, amylase; L, lipase.

men with a Leeds and Northrop pH meter, using a thimble-type sample holder.*

RESULTS

Table I shows the figures obtained from the enzymatic analysis of the 126 specimens from sixty-three patients.

Trypsin.—In twelve subjects the tryptic activity of the second specimen was higher than that of the first. In thirteen instances the tryptic activity was lower in the second specimen, and in the remaining thirty-eight patients the levels were the same in the two specimens.

Amylase.—The amylase activity of the second specimen was higher than that of the first in only twenty-one subjects, while it was less in the second specimen in twenty-nine subjects, and the same in thirteen.

Lipase.—In twenty-six patients the lipase level was higher in the second specimen than it was in the first. There were twenty-nine subjects in whom the lipase activity of the second specimen was lower than in the first, and in the remaining eight cases the activity of the two specimens was equal.

pH.—A comparison of the pH determinations shows no real or significant differences in the two specimens, although there were thirty-nine subjects in whom the pH of the second specimen was higher than it was in the first, and in nineteen subjects the pH of the second specimen was actually lower than the first. In the remaining five patients there were no differences in the pH of the two specimens.

DISCUSSION

The sixty-three subjects used in this study were consecutive cases referred for a diagnostic duodenal intubation. The clinical diagnoses recorded in Table I were those of the physician in

*Normals.—Trypsin activity is determined by its effect on 7.5 per cent gelatin substrate incubated for one hour at 37° C., and then refrigerated at 4° C. for twenty-four hours to stop enzymatic activity. The highest dilution in which the gelatin has been liquefied is recorded as the number of milliliters of juice which produced liquefaction of gelatin. The normal value by this method is 32 units or more.

The amylase analysis is based on the formation of maltose from a 1 per cent soluble starch solution by a 1:50 dilution of duodenal juice. The normal value in thirty minutes is 20 mg. or more in infants over 1 year of age. The value for younger subjects is quite variable and usually lower than the 20 mg. figure.

Lipase assay is determined by the degree of acidity produced when 1 c.c. of duodenal juice is incubated for twenty-four hours at 37° C. with 2 c.c. of olive oil. The acidity is determined by titrating the mixture with 0.1 NaOH, and the result is reported as the number of milliliters of 0.1 NaOH necessary to neutralize the fatty acids formed by the lipolytic activity of 1 c.c. of duodenal juice. The normal value is 10 ml. or more of 0.1 N NaOH.

charge of the case. None of the patients were acutely ill and all of them were in a satisfactory state of hydration, although some of the cases were intubated during hot summer months. There were no ill effects noted that could be attributed to the procedure. Studies on the blood electrolytes were not done since it was not felt that they would contribute any information relative to the purpose of the study. Also, no attempt was made to estimate the amount of gastric juice or to determine its chemical composition, since this subject has been thoroughly reviewed by other workers.[10] The amount of saliva secreted during the procedure obviously could not be accurately measured.

In view of the normal anatomic variations and the gastric configurations of infants,[11] it seems unlikely that all of the gastric contents could be completely removed from the stomach by the gastric tube, since the tubes were not manipulated to different positions for fear of displacing the duodenal tube from its desired position.

The results obtained by analysis of the duodenal specimens taken before and after gastric aspiration showed surprisingly little difference in the pH value or enzyme contents of the two specimens. It will be seen from Table I that where there was a difference it was negligible. A comparison of pH values of the two specimens suggests that if gastric juice enters the duodenum while the tube is in place it is neutralized by the alkaline duodenal juice. Thus, there were only thirty-nine instances in which a second specimen was more alkaline than the first. There were nineteen instances in which pH figures were indicative of more acidity in the second specimen, which theoretically contained less gastric juice than the first.

Appraisal of the tryptic activity of the duodenal specimens before and after gastric drainage showed no differences that could not be accounted for by the normal fluctuations of trypsin content of duodenal juice, since gastric juice does not contain trypsin. The same reasoning could be applied to the figures for lipase, although Davison[12] has stated that the gastric juice of infants contains a weak lypolytic enzyme.

There were six patients in whom one of the trypsin values was lower than the normal figure. However, a follow-up was made on these children and none developed clinical evidence of cystic fibrosis of the pancreas.

There were ten patients in the series with a clinical diagnosis of idiopathic celiac disease. This was the diagnosis of the pediatrician in charge of the patient, based on the clinical findings and course of the disease. Of the twenty analyses of these ten patients, five were slightly less than normal, and only one was abnormally low, which was from a 6-month-old infant. Pancreatic amylase levels are characteristically low in infants during the first six months of life.[3-7] There were seventeen infants in this study who were not more than 6 months of age, and the amylase figures in these infants showed a mean of only 7.6 units in the first specimen and 5.2 units in the second specimen.

McDougall[6] has shown that pancreatic enzyme secretion is sometimes considerably depressed during an acute and severe illness. None of the patients in this study were acutely ill when intubated. Andersen[7] has demon-

strated that normal gastric juice can destroy salivary amylase, and that the gastric juice of idiopathic celiac patients often lacks this capacity during the critical stage of their disease, but regains it when the patients return to a state of good health. None of the patients in this report were intubated during a critical period of celiac disease.

There were seventeen infants in this study who were not more than 6 months of age. The amylase figures in the specimens before and after gastric aspiration were significantly lower than those of the older patients. That salivary amylase can reach the duodenum in substantial amounts is suggested by the high levels obtained in the duodenal juice of eight selected

TABLE II. ENZYMATIC ANALYSIS OF DUODENAL JUICES OF EIGHT PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

INITIALS AND AGE	FINAL DIAGNOSIS	ROUTINE DUODENAL SPECIMEN NO. 1			
		T*	A*	L*	pH
1. E. W. 15 mo.	Cystic fibrosis of pancreas	0	12	0	7.3
2. R. H. 9 yr.	Cystic fibrosis of pancreas	0	32	0	7.8
3. T. McC. 1 yr.	Cystic fibrosis of pancreas	0	14	1.5	7.8
4. A. L. 13½ yr.	Cystic fibrosis of pancreas	0	17	0	7.6
5. F. Z. 2 mo.	Cystic fibrosis of pancreas	0	18	0	8.2
6. F. L. 11 mo.	Cystic fibrosis of pancreas	0	20	0	8.1
7. A. McM. 6½ yr.	Cystic fibrosis of pancreas	0	18.4	0	7.5
8. D. H. 28 mo.	Cystic fibrosis of pancreas	0	40	1	7.4

*T, Trypsin; A, amylase; L, lipase.

That it is at least possible for some salivary amylase to reach the duodenum unchanged is suggested by the figures in Table II, from eight patients with cystic fibrosis of the pancreas. None of the duodenal specimens from these patients contained trypsin and only two showed faint traces of lipase activity. The range for amylase activity was between 12 and 40. These patients had only the customary duodenal intubation and gastric juice was not aspirated. It is assumed that the amylase figures in these cases resulted from swallowed saliva that had entered the duodenem unchanged, since no patients with cystic fibrosis of the pancreas have been reported in whom only amylase secretion occurs.

patients with cystic fibrosis of the pancreas. The levels of trypsin and lipase in the sixty-three patients showed no significant differences in the duodenal specimens before and after gastric aspiration. The pH figures do not reflect any consistent differences in the specimens before and after gastric aspiration.

It is concluded from this study that it is not necessary to attempt to prevent gastric juice from entering the duodenum during the collection of the duodenal sample for enzymatic analysis.

SUMMARY AND CONCLUSIONS

A diagnostic intubation was performed on sixty-three patients between

the ages of 1 month and 11 years. None of the subjects had cystic fibrosis of the pancreas.

Fasting duodenal specimens were collected before and after the stomach was emptied and kept as empty as possible with gentle suction by syringe. The duodenal specimens were analyzed for trypsin, amylase, and lipase, and a pH determination was made on each specimen.

There were ten patients in the group who had a clinical diagnosis of idiopathic celiac disease. The amylase figures in the second specimen of duodenal juice were not significantly lower than in the first specimen.

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SOME COMMENTS ON ACNE VULGARIS IN ADOLESCENTS

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THERE is little that is new about acne or its treatment but it is helpful to review what we do know, to re-emphasize important points, and to consider not only the ailment itself, but also the kind of person who has it, *his* (or her) characteristics, and how these affect the illness and its management.[1, 2] This paper comments upon matters related to acne and includes some cross-sectional data concerning its incidence and its relationship to chronological age, skeletal age, and emotional status.

Acne is significant because it is very common and because of its impact on the patient's personality. However, the adolescent tends to reject any suggestion that there is anything wrong with his body and may not seek help; and some physicians, either pessimistic regarding their ability to modify the acne or thinking that it will disappear, give it and their patient too little attention.

Satisfactory management includes a knowledge of the patient's personality, as well as of the therapy of the disease itself. It is important to understand adolescents' embarrassment, how they feel about their bodies, why they may feel guilty, why they may need your support. To treat them satisfactorily it is as necessary to know them as it is to know their disease. Your approach to them and your thinking about them should be different from that you would use either with a child or with an adult.[3] See your patient alone; his or her parents, when interviewed, should see you at another time. Give him a chance to talk and to ask *you* questions. Show an interest in *him*, as well as in his complaint.

It is necessary to encompass the patient's total personality and to make him feel your interest in him. A few minutes spent inquiring about hobbies, school, social interests and activities will help to establish the sort of relationship which will make it easier for him to discuss his ailment and his fears, and later to accept your suggestions. The burden of adhering to treatment is put up to the patient, not to the parents. Constructive help is offered: the problem is never minimized or put off with a casual "You will grow out of it; forget it." Be factual in your explanations, but not unduly pessimistic. If the patient seems overly anxious, suggest an earlier return visit than you would because of the skin condition itself.

INCIDENCE

Data concerning the incidence of many ailments common in adoles-

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cence, particularly the minor ones, such as avulsion of the tibial tubercle, dysmenorrhea, plantar warts, or acne, need critical evaluation. Hospital statistics can be misleading, for only a small proportion of the people who have these and similar difficulties seek hospital outpatient care and so few consult specialists that incidence data derived from their practice cannot be valid. Cross-section or well-planned random-sample studies, of which there are few, can be expected to yield the best information.

During the three years from 1952 through 1954, 1,795 different boys and girls ranging in age from 12 to 21 years were seen in the Adolescent Unit. It had not been previously contemplated that their records would be reviewed for comments regarding acne, and therefore the judgments regarding this condition were neither made nor recorded with meticulous care. However, "acne" is part of the physical examination check list, and also, since this ailment is peculiar to the adolescent, it is reasonable to assume that the records have better than average accuracy. About 85 per cent of these patients had no acne or acne in such a mild form that it did not constitute a problem either physically or emotionally. Twelve per cent had acne which was classified as moderate to severe and 3 per cent had severe cystic acne. These data are presented as indicating the incidence of acne *in this clinic*, not *in adolescents*.

Other data of a cross-sectional nature yield more valid information. At a boys' boarding school, 357 members of three successive entering classes (of about 120 members each) were studied during their stay.[4] Records of such data as their general health, skeletal age, secondary sexual characteristics, and emotional status were kept. Maturation ratings were assessed by Greulich and colleagues[5] according to the criteria they have described. Skeletal age determinations were based on evaluations of hand-wrist roentgenograms.[6] Acne was rated as severe, moderate, slight, or nonexistent.

TABLE I. INCIDENCE OF ACNE AMONG 357 BOYS EXAMINED AT VARIOUS CHRONOLOGICAL AGES

	CHRONOLOGICAL AGE							TOTAL
	12	13	14	15	16	17	18	
No acne	3	54	187	164	74	9	0	491
Slight acne	0	2	7	11	15	4	0	39
Moderate to severe acne	0	4	20	39	24	4	0	91
Total examinations	3	60	214	214	113	17	0	621
Per cent with acne	0	10.0	12.6	22.3	34.4	47.0	0	20.9

Table I indicates an increase in the incidence of acne as chronological age increases, with acne occurring in about 10 per cent of adolescents at ages 13 and 14, with a rise to about 22 per cent at age 15, and to 34 per cent at age 16. That the process of growing older and maturing is related to acne is further shown in Table II. Here, a difference is seen in the incidence of acne at the same chronological and skeletal ages: the incidence of acne is lower at skeletal ages 13, 14, and 15 than it is at the corresponding chronological ages. That degree of maturation is a factor

is further evidenced by the data in Table III. There was little or no acne in the sexually immature boys, but it occurred in about 30 per cent of those whose maturation was similar to that of an adult.

This same material also furnishes some data which bear on the question as to whether the incidence of acne is higher among emotionally disturbed adolescents. Although it is difficult to conceive that anxiety and tension do not adversely affect acne, there is no indication in this survey that those boys whose emotional state required their withdrawal from school or required psychotherapy during their stay were more likely to have acne than their better-adjusted fellow students. Out of a total of 359 boys, fifty-one were classified as having definite emotional difficulties. Over a two-year period, 26 per cent of the well-adjusted boys and 22 per cent of the emotionally disturbed boys developed acne. During the next two years many boys dropped out of school, but of the twenty-one poorly adjusted boys who were observed over a four-year period 41 per cent developed acne, as compared with 36 per cent of the well-adjusted group. It would seem clear that the more severe emotional disturbances of adolescence are not major factors in the production of acne.

Table II. Incidence of Acne Among 357 Boys Examined at Various Skeletal Ages

	SKELETAL AGE							TOTAL
	12	13	14	15	16	17	18	
No acne	10	53	143	127	90	48	20	491
Slight acne	0	0	4	5	15	9	6	39
Moderate to severe acne	0	1	6	20	37	18	9	91
Total examinations	10	54	153	152	142	75	35	621
Per cent with acne	0	1.9	1.9	16.5	36.8	36.0	43.0	20.9

Table III. Occurrence of Acne at Each of the Greulich[5] Maturation Ratings

	MATURATION RATING					TOTAL
	1	2	3	4	5	
No acne	10	12	63	188	192	465
Slight acne	0	0	2	9	22	33
Moderate to severe acne	0	0	4	23	60	87
Total examinations	10	12	69	220	274	585
Per cent with acne	0	0	8.7	14.5	29.9	20.5

PATHOLOGY

At puberty there is a marked increase in the activity of the endocrine system. In response to higher testosterone levels in boys and progesterone levels in girls the activity of the sebaceous glands increases. This results in hyperplasia of the sebaceous glands, oiliness of the skin, and hyperkeratinization at the orifices of the sebaceous glands. The keratin plugs act as foreign bodies and cause both retention of sebum proximal to the orifices and pressure atrophy of the lining cells of the follicle. The inflammatory changes which accompany this foreign body reaction render the cells of the follicle and the sebaceous apparatus susceptible to bacterial invasion. Sebum formation is greatest where sebaceous glands are most plentiful. Consequently acne is more likely to be widespread on the forehead and back than on the extremities, and can be expected to

increase when androgen production (which increases the number, size, and secretion of the sebaceous glands) is raised.[7]

Inflammatory changes at the follicular orifices may also result from such agents as cutting oils, animal furs, or from the ingestion of halogens, iodides, and bromides. Excessive sweating and accompanying friction may macerate the skin and cause retention of sebum. Pyoderma results when the skin's normal bacterial flora becomes pathogenic. It is most likely to occur, or to become excessively severe, in those individuals whose family history or whose own past history indicates a hypersensitivity to staphylococcal infection. Focal bacterial infection in other organs, or in areas other than the skin, may affect the development of acne. Factors such as fatigue or emotional tension, or such disturbances as anemia may increase the severity of acne.

Mild cases of acne in adolescence consist primarily of oiliness of the skin of the face, chest, and back, with numerous comedones and discrete papules. Many patients have a concomitant seborrhea of the scalp. In more severe acne there are pustules in various phases of evolution, confluent papules, and scarring. The most severe type of acne presents cysts, either of the discrete nodular type, or of burrowing, "ropelike" lesions. In these patients scarring is an important feature.

TREATMENT

Therapy should be instituted as soon as possible, for it is impossible to predict whether the acne will or will not subsequently be accompanied by scarring. Mild acne may be improved by such simple therapeutic measures as frequent and conscientious use of soap and water, careful expression of comedones and local application of sulfur lotions. Any mild, neutral soap will suffice for cleaning, but it should be remembered that one of its chief purposes is the removal of excessive oiliness, and gentle washing of the face should be carried out a sufficient number of times daily to produce this effect. Sulfur alone in varying strengths (such as zinc sulfate 4.0, potassium sulfuret 4.0, distilled water q.s. 120.0, applied morning and night) or in combination (such as precipitated sulfur 3.0, resorcinol 3.0, glycerin 4.0, zinc oxide 6.0, alcohol and water āā q.s. 120.0) will be helpful. Vleminckx's solution, sulfurated lime, diluted (1 to 10 parts of water) may be used before retiring, as hot compresses, for five minutes. This helps to remove comedones and also exerts an antiseborrheic effect. No oily ointments should be used, but if an ointment is indicated, precipitated sulfur 3.0, resorcinol 3.0, kaolin 6.0, zinc oxide ointment q.s. 60.0 may be used. When sulfur preparations prove too irritating or drying, then their use should be restricted to one application daily or once every other day.

Accompanying seborrhea of the scalp may be treated with selenium sulfide or with 3 per cent salicylic acid and 3 per cent precipitated sulfur in petrolatum. Shampooing with sulfonated detergents is preferred; preparations for keeping the hair in place which contain oil should be avoided.

Physical aids employed locally include ultraviolet therapy in suberythema doses given once or twice weekly. X-ray may be given once

weekly to each area, over a period of eight to twelve weeks, in a dose not to exceed 60 r. at each treatment, and *should be administered by a qualified dermatologist or roentgenologist.*

Trauma in any form, face picking, squeezing, or rubbing, as with a complexion brush, should be avoided.

In more severe cases, especially those with pyoderma, an attempt to control the infection by the systemic use of tetracycline or oxytetracycline in oral dosages ranging from 250 to 1,000 mg. daily is justified. These drugs should not be continued more than ten days, although repeated courses may be necessary to control recurrences. Antibiotics applied locally have given inconsistent results and are not recommended. Vaccine therapy with staphylococcus toxoid or autogenous staphylococcus vaccines is occasionally helpful.

If the patient's history suggests that any of the following foods are factors, they should be eliminated from the diet: chocolate, nuts, seafood, coffee, pork, candies, fried foods, and any others which the patient believes to be deleterious. It is to be remembered, however, that foods are neither a consistent nor a major factor in this ailment.

It is important to regulate hygiene and insist on a planned program of adequate exercise. Focal infection should be remedied by appropriate means.

Various techniques, as sandpapering or surgical planing, have been devised to treat scarring.[8] The possibility that granuloma may result,[9] and the fact that an improvement in the skin's appearance will not necessarily better a maladjusted patient's outlook on life (it may even make it worse[10]) should make one hesitant to recommend dermabrasion. It should never be used when acne is active, and is a procedure best left to an expert. Those whose experience is greatest are most likely to reject more applicants than they accept.

SUMMARY

The importance of acne to the adolescent is commented upon and the desirability of treating and understanding him or her, as well as the disease, is emphasized.

Data indicating the association of acne with the process of maturation and showing little relationship to emotional disorders are presented.

The pathology and treatment of acne are reviewed and commented upon.

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THE RELATIONSHIP OF PARANATAL EXPERIENCE TO OXYGEN SATURATION IN NEWBORN INFANTS

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PIONEER work in the determination of the oxygen saturation of the "fetus at the moment of birth" was done by Eastman,[1] working with rather large specimens of cord blood. The development of techniques using small samples of blood has enabled subsequent investigators to gather additional data on the oxygen economy of the newborn infant and its relationship to obstetrical procedures. Significant contributions to our body of knowledge have been made by Clement Smith[2] with several co-workers, by Taylor,[3] Watts,[4] and Montgomery[5] and their associates. More recently, long-term studies relating blood oxygen levels in early neonatal life to subsequent neurological status have been initiated by MacKinney and his colleagues,[6] and by Apgar[7] and her co-workers. Such studies attempt to estimate the role of neonatal oxygenation and documented obstetrical experience in the production of brain damage.

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This study was initiated by a four-month grant from the Frances Israel Fund of the Noshin Rachmonioth Society of St. Louis, Mo. From Nov. 1, 1953, to No. 1, 1954, it received partial support from the Children's Research Foundation, St. Louis, Mo. From Nov. 1, 1954, it has been supported by Research Grant B685 from the National Institute of Neurological Disease and Blindness, of the National Institutes of Health, U.S. Public Health Service.

Our study embraces two aspects: first, to secure further information regarding the effect of obstetrical variables on oxygen saturation at birth and during the first hour of extrauterine life, and, second, to relate both oxygen levels and obstetrical experience to neonatal and later behavior as measured by psychometric and medical examination. Only the first will be considered in this report.

MATERIAL AND METHODS

Subjects.—The subjects were 323 infants delivered vaginally, 276 of whom were born in the St. Louis Maternity Hospital, a large teaching hospital. This group includes both white and Negro, private and clinic patients. Forty-seven infants were born at the Homer G. Phillips Hospital, a city-supported hospital for Negroes. Blood samples from these latter infants were collected during March and April of 1955, but data on the Maternity Hospital group was gathered sporadically between July, 1953, and November, 1955. The cases were essentially unselected, depending primarily on the ability of one of the investigators to be present at the delivery; hence, most were born during the daytime hours. In those instances where a choice had

to be made between two simultaneous deliveries the one most likely to involve complications was chosen.

No attempt was made to influence or standardize obstetrical procedure in any way. No prescriptions regarding the type or amount of anesthesia or analgesia were made. The individual obstetrician used his own technique concerning the reservoir of placental blood, in most instances clamping the cord after the vessels had stopped pulsating. Since we view immediate clamping of the cord as possibly prejudicial to the infant, we did not wish to impose this practice as a condition of study. Our interest then was in the observation of neonatal oxygen levels with respect to prevailing obstetrical custom. Although this lack of standardization increases the number of variables and does not give us equal numbers of cases in the different groups, we felt that by such a procedure as much could be learned and more cordial cooperation obtained than were any attempts made to dictate to another service.

Collection and Analysis of Blood Samples.—Where possible, four samples of blood were taken from each infant. The first of these was the cord specimen taken at the time of delivery. The obstetrician clamped the cord long and the sample was withdrawn by a tight-fitting syringe from the umbilical vein, the cord reclamped at the usual site, and the small amount needed discharged at once under oil in the special heparinized collecting tube. Three subsequent cutaneous or "capillary" specimens were taken from the heated heel at 10, 30, and 60 minutes following birth. Usually the first two samples were taken in the delivery room and the last two in the newborn nursery. Collection consists essentially of first heating the foot in a sterile diaper wrung out of hot water, followed by a brisk stab with a new No. 11 Bard-Parker blade. The heel is then lightly coated with sterile mineral oil (to channel the drops neatly into the tube without smearing and exposure to air) and the drops allowed to fall quickly through oil in a short, small heparinized test tube held within a centimeter of the prick. Lilienthal and Riley[8] have shown this momentary exposure to air not to affect the oxygen content of the blood. The tubes are kept iced until the series for the infant is complete, then analysis is performed. Numerous reports[2, 9, 10] confirm the reliability of capillary blood as a measure of arterial oxygen saturation. In our babies the cyanosis of the feet often seen in newborn infants was not apparent at the time of punctures since the preliminary heating results in universally pink heels and also increases the vasodilatation so that a deep cut is unnecessary. The pricks are sufficiently atraumatic that babies on the private service could be used without apology.

The method of analysis was a microadaptation[11] of the spectrophotometric determination of oxyhemoglobin described by Roos and Rich.[12] Although the accuracy of this method may be less than that of the microgasometric technique it is probably as great as that of the ear-lobe oximeter. It was therefore considered applicable for the study of the considerable number of cases, with several observations on each infant.

TREATMENT OF DATA

Cases were classified according to strength of analgesia, type of anes-

thesia, and the presence or absence of obstetrical and prenatal complications.

Analgesia.—Because of the large number of obstetricians participating, no single scheme of analgesia was used. The analgesic drug appearing most frequently is Demerol, with or without hyoscine, barbiturates occurring only occasionally in the series. Trichlorethylene used a la reine during the first stage appears not infrequently and thus used is classified as an analgesic. Taylor and associates[13] have shown recently that this agent so used does not depress oxygen saturation from the normal. After due consideration we arbitrarily categorized premedication as follows:

"No" or "Light"

1. No premedication other than hyoscine within four hours of delivery.
2. Demerol, 50 mg. intramuscularly within four hours of delivery.
3. Trilene inhalations with contractions only, administered by the mother herself, with or without Demerol as specified above.

"Moderate"

1. Demerol, more than 50 mg. intramuscularly within four hours of delivery (average dosage, 100 mg.).
2. A combination of a barbiturate with 50 mg. of Demerol within four hours of delivery.
3. Either of the above with Trilene.

In twenty-one of the 323 cases something over 100 mg. of Demerol was given within four hours of delivery, but since this number of cases was not large enough to treat separately, they were included in the "moderate" group. Perhaps unfortunately for purposes of investigation but as evidence of prevailing obstetrical custom in our series, there were almost no cases of true oversedation.

Anesthesia.—Several types of anesthesia were employed in these deliveries. These were continuous caudal, pudendal block only, and the inhalation of nitrous oxide-oxygen, nitrous oxide-oxygen-ether, and chloroform, distributed as shown in Table I. Deliveries in which no anesthesia was used were classified with the pudendal block only. There would be no reason to expect a pudendal block to have any more effect on the oxygenation of the infant than a birth without anesthesia. An analysis of the data revealed that the groups did not, in fact, differ. The inhalation anesthetic most often used was a nitrous oxide-oxygen mixture in proportions of 80:20 per cent. Chloroform was used infrequently. Cases in the inhalation group may or may not have had pudendal block in addition to the inhalant.

TABLE I. DISTRIBUTION OF ANESTHETICS IN 323 VAGINAL DELIVERIES

ANESTHETIC	UNCOMPLICATED CASES	COMPLICATED CASES
Nitrous oxide-oxygen	96	29
Gas-oxygen-ether	30	11
Chloroform	15	8
Pudendal block or none	68	21
Continuous caudal	35	10
Total	244	79

The largest inhalant group, nitrous oxide-oxygen, with ninety-six uncomplicated cases, was subdivided into a "light" group which included: "whiffs" at the end of the second stage, intermittent gas with contractions, and five minutes or less of continuous anesthesia prior to delivery; and a second group receiving over five minutes of continuous anesthesia. With the strength of analgesia taken into account there was no significant effect from the longer anesthesia. This is probably a valid observation since these were uncomplicated cases in which anesthesia was held to the obstetrical rather than the surgical plane,

the depth of anesthesia being no more than that compatible with delivery by episiotomy and low forceps. It is unfortunate, however, that we did not fully appreciate the unreliability of the anesthesia records until the study was well under way, for although the pediatrician collecting blood samples kept a log of events, this was not done with a stopwatch, and we have concluded that such timing lacked the degree of accuracy necessary for further breakdown in this area.

Complications.—Cases were divided into three groups with respect to complications. These were (1) uncomplicated, with negative prenatal history and low forceps or spontaneous delivery, 244 infants; (2) fetal complications, including difficulties of labor, but with the delivery itself normal, 25 infants; (3) cases with abnormal or operative delivery, whether or not prenatal complications were also present, 54 infants. The criterion for inclusion in Group 2 or 3 was the existence of one or more conditions or factors anticipated to prejudice the infant with respect to oxygenation. Although fundal pressure has long been an accepted means of effecting delivery, we questioned its inclusion with a group of completely uncomplicated deliveries. Our decision to classify it with other delivery complications was, in fact, justified by a significantly lower cord blood oxygen in the sixteen cases in which fundal pressure was used. Complications encountered are shown in Table II.

TABLE II. COMPLICATIONS OF DELIVERY ENCOUNTERED IN OUR SERIES

FETAL COMPLICATIONS	NO. OF TIMES ENCOUNTERED ALONE OR IN COMBINATION
Pre-eclampsia	13
Meconium staining of infant or fluid (excluding breech)	5
Cord tight around neck	5
Prolonged labor without progress	4
Uterine inertia	3
Rapid hard labor	3
Notably infarcted placenta	2
Placenta previa or other bleeding during third trimester	2
Diabetes mellitus	2
Eclampsia	1
Premature separation of placenta	1
Sickle-cell anemia (with crisis prior to delivery)	1
Anemia, hypochromic	1
Erythroblastosis fetalis	1
Hyperemesis, associated with hypertension and anemia	1
Abnormal fetal heart rate	1
Chronic nephritis with renal insufficiency	1
Premature rupture of membranes	1
COMPLICATIONS OF DELIVERY	**NO. OF TIMES ENCOUNTERED ALONE OR IN COMBINATION**
Fundal pressure*	16
Breech	14
Prematurity	9
Forceps rotation	7
Precipitous delivery	5
"Difficult" low forceps	3
Shoulder dystocia	2
Midforceps	2
More than average traction necessary to effect delivery	2
Twin birth	1

*See text under "Complications."

Other Factors.—Several other factors were considered in determining the treatment of results. The samples obtained from the two hospitals did not differ significantly from each other and thus were pooled for analysis. In forty-eight instances maternal oxygen was given prior to or during delivery. In most cases this was of short duration, following the birth of the head and before the cord was cut, but subsequent to various anesthesias. These forty-eight cases did not differ significantly from a control group equated for other factors and hence have been included with the rest of the sample. Primiparity has been excluded as a factor explaining our results since primiparas and multiparas appear to be equally distributed in the various groups compared.

Statistical Analysis.—The statistical technique employed in most of the following analyses was analysis of variance using Snedecor's[14] method of weighting for disproportionate subclass frequencies. This permitted the simultaneous determination of the effects of two factors and the interaction between them, using all cases even where there were large numbers of subjects in one category and relatively few in another. When the following text states that a difference was "significant statistically," it means that a difference as large as the one obtained would be expected by chance only five times in 100, or less often. This is the usual $P = 0.05$ level of significance.

RESULTS

Arterial Oxygen Saturation as a Function of Analgesia, Anesthesia, and the Obstetrical Situation.—The span of observed oxygen saturations in the four samples (cord, 10, 30, and 60 minutes) in 244 uncomplicated vaginal deliveries is shown in Fig. 1. Since oxygen for resuscitation might be expected to affect directly the blood oxygen saturation subsequent to its administration, the nine infants of the uncomplicated deliveries thus treated are not included in the figure beyond the initial cord sample. As can be seen, the range in cord samples is a wide one, a few cases with values as low as 10 to 19 per cent occurring in this normal group. Smith and Kaplan[2] in 1942 observed no consistent relationship between the level of oxygen in the cord blood and the rate of change after birth, and this was substantiated by Taylor and associates[3] in 1951. Thus the infant starting off with a truly hypoxic cord sample may recover with amazing rapidity, and, by the same token, the infant who is born with a normal or high oxygen level is not guaranteed, a priori, against the development of secondary apnea and anoxia. By ten minutes most babies have oxygen levels above the 50 per cent level, the majority being between 70 and 100 per cent, while by 30 minutes, more than half of the babies are already normally oxygenated (90 per cent or over saturation being considered normal for the neonate). By 60 minutes only about one-fifth of the infants are still below this level.

Table III presents the uncomplicated deliveries grouped for the two strengths of analgesia previously mentioned, and according to the type of anesthesia used. As in Fig. 1, the nine oxygen resuscitated cases are included only for the cord sample. Differences in numbers of cases in each sample arose because not all four speci-

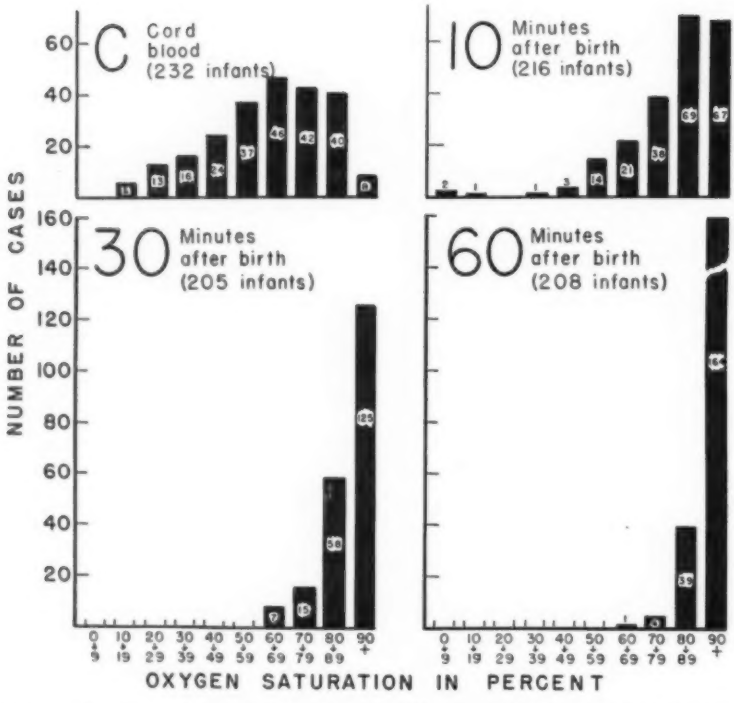

Fig. 1.—The span of oxygen saturations in 244 uncomplicated vaginal deliveries.

TABLE III. EFFECT OF ANALGESIA AND ANESTHESIA ON ARTERIAL OXYGEN SATURATION OF THE NEWBORN INFANT IN 244 UNCOMPLICATED VAGINAL DELIVERIES

TIME OF SAMPLE	ANALGESIA	PUDENDAL OR NONE	CONTINUOUS CAUDAL	NITROUS-OXIDE OXYGEN	NITROUS OXIDE-OXYGEN-ETHER	CHLOROFORM	TOTAL MEANS
Cord	Light N	47	26	54	8	3	N = 232
	Mean	70.0%	60.9%	60.6%	60.0%	56.0%	61.3%
	Mod. N	15	9	39	20	11	
	Mean	62.5%	46.1%	62.3%	51.3%	57.0%	
10 min.	Light N	43	23	54	8	3	N = 216
	Mean	87.9%	76.4%	79.1%	84.8%	85.0%	80.8%
	Mod. N	17	8	32	19	9	
	Mean	84.8%	84.9%	79.0%	84.9%	63.1%	
30 min.	Light N	40	22	52	7	3	N = 205
	Mean	90.9%	87.4%	88.9%	94.6%	88.0%	90.1%
	Mod. N	14	9	33	18	7	
	Mean	99.4%	89.2%	91.9%	90.3%	95.0%	
60 min.	Light N	42	23	50	9	3	N = 208
	Mean	95.5%	92.7%	93.1%	93.7%	95.0%	94.2%
	Mod. N	14	8	32	18	9	
	Mean	95.3%	91.5%	94.5%	94.9%	95.9%	

mens could be obtained from every infant. It will be observed that the pudendal block group is better oxygenated initially and during the first hour than any of the inhalant groups or the continuous caudals. Differences among these groups are statistically significant for the cord and 10-minute samples. At 30 and 60 minutes, anesthesia no longer has a statistically significant effect, although there is still a difference in favor of the group receiving regional or no anesthesia. The mean differences between anesthesia groups and the probabilities that they could have arisen by chance are shown in Table IV. Since the number of chloroform cases is not sufficiently large to permit statistical treatment, these are not included in Table IV.

Analgesia does not have such a clear-cut effect, although it should again be emphasized that our sample includes very few infants who were heavily premedicated. As can be seen in Table IV the relatively better oxygenation of cord blood when only light analgesia is used is not statistically significant at the usual 0.05 probability level, although the trend suggests that a truly heavily premedicated group would be worth investigation. By 10 minutes and later, premedication shows no appreciable effect on oxygen saturation.

Cord blood values in uncomplicated cases ranging from 43 to 68 per cent have been reported by Watts and collaborators,[4] MacKinney and co-workers,[6] and Taylor and associates.[3] Our values range from 46 to 70 per cent, with an average of 61 per cent. Differences in particular anesthetic groups are difficult to assess because of variations in technique of administration. It should also be pointed out that two-thirds of our infants received less than half the amount of premedication given to all Taylor's subjects.

Figures subsequent to the cord sample as reported by MacKinney also closely resemble ours. Taylor's, however, are consistently lower. We suspect that this may be because MacKinney's method of earlobe oximetry is actually more similar to ours in that the oximeter induces vasodilation, accomplished in our case by heating the heel. Taylor does not mention heating the heel prior to collection. It is possible that the unheated heel may not reflect with uniform accuracy the arterial oxygen saturation during the first hour of life inasmuch as many neonates experience some degree of hypothermia with accompanying sluggish peripheral circulation. On the other hand, Apgar and associates[7] believe that cyanosis of the feet makes no particular difference.

TABLE IV. MEAN DIFFERENCES IN PER CENT OXYGEN SATURATION IN UNCOMPLICATED DELIVERIES AS A FUNCTION OF ANESTHESIA AND ANALGESIA AND PROBABILITY THAT THESE DIFFERENCES ARE DUE TO CHANCE

	LIGHT VS. MODERATE ANALGESIA		REGIONAL ANESTHESIA VS. TWO INHALANTS AND CAUDAL ANESTHESIA	
TIME OF SAMPLE	DIFFERENCE FROM MEAN	PROBABILITY IN 100 OF A CHANCE DIFFERENCE (P)	DIFFERENCE FROM MEAN	PROBABILITY IN 100 OF A CHANCE DIFFERENCE (P)
Cord	7.3	5-10	9.4	1
10 min.	0.3	Over 50	6.0	1
30 min.	−2.2	Over 50	4.8	5-10
60 min.	0.3	Over 50	2.0	10-20

Differences are estimated by averaging means of the appropriate subgroups of Table I rather than by averaging without regard to subgroup classification.

No attempt has been made to determine the effect of analgesia and anesthesia in complicated cases although here it might be most meaningful. The size of the group and the problem of equating differences in kind and degree of complication does not warrant such treatment. It was possible, however, to make comparisons between complicated and uncomplicated groups as a whole. In order that these comparisons would not be invalidated by differences in anesthesia and analgesia, the variance due to these factors was removed statistically.

both groups. When the delivery situation was difficult, however, the cord blood oxygen saturation dropped to 53.6 per cent. A difference as large as this is significant. It would be expected by chance only one time in 100. These results agree with Smith and Kaplan's[2] statement that "the oxygen economy of the fetus at the moment of birth cannot be taken as representative of the physiological status which has obtained until that time in fetal life." Oxygen levels at this moment apparently *do*, however, reflect events of the birth process itself. By 10 minutes,

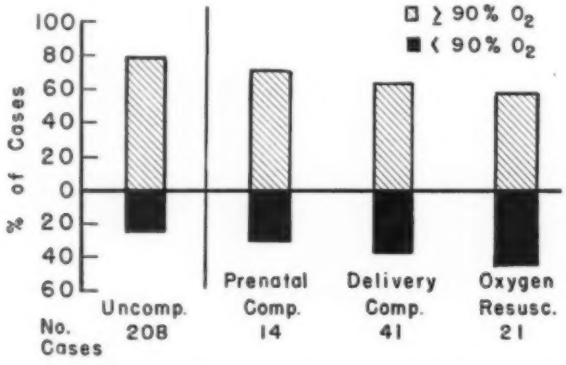

Fig. 2.—Percentage of infants achieving normal (90 per cent or over) oxygen saturation by one hour of life.

In Table V the mean oxygen saturation values of the total uncomplicated group is compared with the two complicated groups: the group with difficulty prenatally or during labor but with normal delivery, and the group for whom delivery itself was abnormal whether or not prenatal complications were also present. There was no difference in oxygen saturation between the two groups where delivery was normal, even though there had been prenatal complications. The cord blood was 61 per cent saturated in no appreciable difference among the groups is apparent when mean oxygen values are considered.

If the criterion of recovery used by others[3] is employed, however, that is, the frequency of cases failing to reach 90 per cent saturation by one hour, the uncomplicated group is far superior. Fig. 2 shows that while only 21 per cent of the uncomplicated group fail to attain this level, 29 per cent of the prenatally complicated and 37 per cent of the delivery-complicated groups fail to reach 90 per cent satura-

tion by one hour.* Oxygen-resuscitated cases (not included in the previous analyses except for the cord sample) are presumably in more precarious condition and Fig. 2 also shows that even with the administration of oxygen, 43 per cent of them are still below the normal 90 per cent level at one hour. Table VI shows their inferior oxygenation throughout the first hour. Mean values are lower for all four samples of blood, with one exception, than those shown in Table V for comparable groups who did not require oxygen resuscitation.

In summary, then, it appears that the oxygen saturation of the fetus and newborn infant is definitely influenced by the type of anesthesia given the mother and by the events of the delivery itself. Prenatal complications alone are not reflected by the blood oxygen saturation values in this series.

TABLE V. PER CENT OXYGEN SATURATION IN UNCOMPLICATED AND COMPLICATED GROUPS

TIME OF SAMPLE		UNCOMPLICATED 244 CASES	PRENATAL-COMPLICATED DELIVERY-UNCOMPLICATED 25 CASES	DELIVERY-COMPLICATED PRENATAL-±COMPLICATED 54 CASES
Cord	N	232	21	48
	Mean	61.3	61.1	53.6
10	N	216	15	44
	Mean	80.8	82.3	81.4
30	N	205	16	42
	Mean	90.1	90.4	90.4
60	N	208	14	41
	Mean	94.2	94.1	92.9

TABLE VI. PER CENT OXYGEN SATURATION OF TWENTY-FIVE INFANTS REQUIRING OXYGEN RESUSCITATION FOR PRIMARY OR SECONDARY APNEA

TIME OF SAMPLE		UNCOMPLICATED	PRENATAL-COMPLICATED DELIVERY-UNCOMPLICATED	DELIVERY-COMPLICATED PRENATAL-± COMPLICATED
Cord	N	8	6	7
	Mean	47.8	49.0	34.4
10	N	7	7	3
	Mean	70.7	62.9	57.3
30	N	7	8	6
	Mean	83.1	83.4	88.2
60	N	6	9	6
	Mean	87.2	88.9	93.3

*The delivery-complicated group is significantly poorer at the 0.05 level than the uncomplicated group, but there is no difference between the prenatally complicated and the uncomplicated group. Chi-square was used, in this and the next section, to estimate the probability that differences could have occurred by chance.

Evidence in favor of smaller amounts of analgesia is suggestive but not conclusive.

Clinical Condition as a Function of Analgesia, Anesthesia, and the Obstetrical Situation.—The effect of these factors may also be considered from the point of view of clinical condition of the infant. We used several criteria in deciding that the clinical condition of the infant was not "normal." First, the use of oxygen for resuscitation

suggests an infant in relatively poor condition since oxygen was not given routinely to infants born vaginally. Second, in addition to babies resuscitated with oxygen, there are those revived by other means. Third, there is a group whose initial condition in the delivery room was not considered optimal. These latter infants exhibited such signs as depression, somnolence, unusual pallor or cyanosis, hypo- or hypertonicity, or abnormal respiration even though spontaneously initiated.

Among the 244 uncomplicated deliveries there was a total of thirty-four such infants, nine requiring oxygen resuscitation and twenty-five whose condition was in some way unsatisfactory at birth or in whom other resuscitation techniques were used. This is an incidence of 14 per cent. These cases did not occur with significantly greater frequency in any one of the anesthesia groups, nor did the pudendal block group show any significant advantage when compared with other groups. The numbers of cases in the various groups, however, is small and when measurement is made simply by frequency count as in this instance, statistically significant differences will not be revealed unless the effect is very marked. When anesthesia groups are combined, as in Table VII, to compare the varying amounts of premedication, the difference in favor of the "light" premedication is significant at the 0.01 level in the uncomplicated group. Although "light" premedication was also superior in both complicated groups, we did not consider this to be conclusive. There is no assurance that the kinds and degree of complications are equated for the two strengths of premedication.

Table VII also shows that when the obstetrical situation is complicated either prenatally, at delivery, or both, babies requiring oxygen resuscitation or in otherwise unsatisfactory condition are seen with much greater frequency. There were fourteen (56 per cent) of the twenty-five infants with a history of prenatal complications and twenty-one (39 per cent) of the fifty-four babies where the delivery situation, alone or in combination with abnormal prenatal history, was complicated. Thus of the babies in the combined complicated groups nearly half were noted to behave abnormally at birth. It might be of interest to mention here that in both normal and complicated categories there were no babies who failed to breathe spon-

TABLE VII. POOR CLINICAL CONDITION AT BIRTH AS A FUNCTION OF OBSTETRICAL SITUATION AND ANALGESIA

OBSTETRICAL SITUATION	ANALGESIA GROUP		BABIES REQUIRING RESUSCITATION OR UNSATISFACTORY AT BIRTH	
			NUMBER	PER CENT
Uncomplicated	Light or none	144	12	8
	Moderate	100	22	22
Total		244	34	14
Fetal complications	Light or none	17	9	53
	Moderate	8	5	63
Total		25	14	56
Complications of delivery (fetal)	Light or none	39	11	28
	Moderate	15	10	67
Total		54	21	39

taneously in the continuous caudal group, although mean cord blood oxygen values of caudal babies were no higher than those delivered under inhalant anesthetics. This absence of apneic infants in caudal deliveries is in keeping with the earlier observations of Masters and Ross,[15] who were able to increase the fetal salvage rate of premature labors in this institution by the use of continuous caudal anesthesia. A lack of constant correlation between cord blood oxygen saturation and initial apnea was also noted by Taylor and associates,[3] though the situation was reversed. Half of his babies delivered under cyclopropane required artificial resuscitation, although the mean cord blood oxygen saturation was as high or higher than that in his other anesthetic groups.

Perhaps the most interesting finding is that while infants with fetal complications did not show a significantly lowered oxygen saturation, they did exhibit other signs of an unsatisfactory clinical status. Our group is too small to consider separately the various kinds of prenatal complications which occurred. It may also be of significance that analgesia appeared to have a more pronounced effect on the clinical condition of the baby than on his oxygen saturation.

DISCUSSION

In an exploratory survey such as this, a large and often confusing mass of data is accumulated. A leading professor of obstetrics recommends to his students that they develop the habit of thinking of the mother's abdominal and uterine walls as transparent, the better to visualize the mechanics of labor and delivery. The reality of such a phenomenon would also be of inestimable value to those responsible for the well-being of the infant once delivery is effected. Failing such a miracle the period of gestation and delivery remains a challenge. Much is being learned, however, by informed observation and documentation of events which, considered alone, seem to lack significance, yet, when inductively interpreted, may assume a form or pattern.

Such a pattern takes shape with respect to the oxygen saturation of the cord blood. We see this saturation to be affected by the type of anesthesia given the mother, to some extent by the type and amount of analgesia given her, and most of all by the existence of complications of delivery. The immediate clinical condition of the infant, on the other hand, seems to be influenced chiefly by abnormalities of the gestational period including labor, though also by complications of the delivery and by the analgesia-anesthesia situation. Studies to be published indicate that fetal complications and immediate clinical condition of the infant are also more closely related to the subsequent neonatal condition of the baby than is oxygenation. This suggests that intrauterine anoxia may be more insidious than a temporary period of anoxia at birth. It is probable that a low oxygen saturation at birth is only one of several important factors and may be of less prognostic value than the existence of certain abnormal behavior patterns during the neonatal period.

One of the questions which our study failed to answer satisfactorily was whether the administration of maternal oxygen consistently raises the oxygen saturation of the infant. Mothers of forty-eight of our babies did receive

oxygen prior to or during delivery; yet when these cases are compared with a control group equated for other factors no superiority of the maternal oxygen group is apparent. We do not feel that any conclusions regarding the value of maternal oxygen can be drawn from these data, as in many cases the oxygen was given for a short time before delivery, in some cases actually following the birth of the head but prior to clamping of the cord. In such cases the placenta may already be separating. Also at this time the strength of the expulsive contractions of the uterus would often interrupt efficient placental circulation. Worthy of mention, however, is the mother with sickle-cell anemia, who was also pre-eclamptic. This patient had been in crisis ten days before delivery but at the onset of labor had a hemoglobin of 10 grams per 100 ml. The mother received pudendal block anesthesia since difficulty with the infant was feared. For the last six hours of labor oxygen was given by nasal catheter, and for the last one-half hour by mask. The baby was born vigorous and unusually ruddy, cried and breathed immediately, and had a cord blood oxygen of 95 per cent. This is the longest period of oxygen administration in our series but there are other infants with unusually high cord saturations whose mothers had received oxygen sufficiently long to be reasonably sure of placental transfer.

It is unfortunate that we were unable to compare the effects of analgesia and anesthesia in the complicated cases, for it is precisely in such cases that these factors are probably most significant. The tolerance of the healthy term fetus to anoxic and other insult is well known; it is in the abnormal situation where a combination of factors may result in a "continuum of reproductive casualty"[16] which may prove damaging or lethal. It would be very useful to have had a group of complications sufficiently large to permit equation not only for kind and degree but with respect to analgesia and anesthesia as well. Although the hazards of equating obstetrical difficulties are obvious, this should not prove impossible where numbers are adequate. For similar reasons we have not included our figures on cesarean sections, but are continuing to gather information which will be treated in a future publication.

Although our findings seem to indicate the relative superiority of regional anesthesia and "light" analgesia with respect to oxygen saturation of the cord blood, we should like to comment on the general excellence of the oxygen economy of this series of infants. There has been some tendency, recently reiterated by the advocates of "natural childbirth" to believe that if a little anesthesia is good none at all is better. Our figures do not support this opinion. They would suggest rather that the type of pain relief afforded by the well-conducted "civilized" delivery is not incompatible with normal oxygenation of the infant.

SUMMARY

The blood oxygen saturation of 323 infants delivered vaginally under varying obstetrical circumstances was studied during the first hour of life. Samples of blood were taken from the cord at birth and from the heel at 10, 30, and 60 minutes.

1. In the series of 244 uncomplicated deliveries, the mean oxygen saturation of cord blood was 61 per cent.

Individual values varied widely, from a few cases with values as low as 10 to 19 per cent to 3 per cent who were already normally oxygenated (90 per cent or over).

2. Low cord values did not preclude subsequent normal oxygenation. The mean values for the uncomplicated cases at 10, 30, and 60 minutes were 81, 90, and 94 per cent, respectively. The per cent of infants who achieved the normal neonatal level also increased rapidly from 31 per cent at ten minutes to 79 per cent at one hour.

3. Of these 244 babies, the group delivered under regional (pudendal block only) or no anesthesia showed oxygen saturation levels in the cord and 10-minute samples superior to those of babies delivered by inhalation anesthetics or continuous caudal. These differences are significant at the 0.01 probability level.

4. In this group of uncomplicated cases, the use of light analgesia resulted in cord oxygen levels superior to those obtained under moderate analgesia. The difference did not reach statistical significance, however.

5. Seventy-nine infants were illustrative of complications of the prenatal period, of the delivery, or both. Prenatal complications alone were not reflected by the cord or subsequent blood oxygen saturation, the mean cord value for twenty-five such infants being the same as that of the uncomplicated group (61 per cent). In the fifty-four cases where the delivery situation itself was complicated (with or without prenatal abnormalities), the mean cord value fell to 54 per cent, a significant difference.

6. When the criterion of normal oxygenation by one hour was used, 21 per cent of the uncomplicated group failed to achieve this level, whereas 29 per cent of the prenatally complicated and 37 per cent of the delivery-complicated groups remained below the normal 90 per cent level at one hour.

7. If the criterion of satisfactory clinical condition at birth was employed, of the uncomplicated group only 4 per cent required oxygen resuscitation and only 10 per cent were in otherwise unsatisfactory condition at birth, a total of 14 per cent. Fifty-six per cent of the prenatally-complicated and 39 per cent of the delivery-complicated group were thus affected.

8. Twenty-five infants requiring oxygen resuscitation were not included in the previous oxygen analyses except for the cord sample. Even with the administration of oxygen, they showed inferior oxygenation throughout the first hour and 43 per cent were still below the normal 90 per cent level at the end of an hour.

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Lancing the Gums for Teething

I sincerely hope the safe and salutary practice of lancing the gums will soon become universal, as I am confident it will save many lovely little sufferers much extreme pain, and most of these alarming complaints. But as I know many very tender mothers are really fearful of having the operation performed by a physician, I must beg them to adopt a mode I have always practised, and which answers a very good purpose, although perhaps not quite so effectual as the regular method. I take a very keen razor and wrap the whole blade in a fine handkerchief, leaving only the extreme point uncovered, (to prevent all danger of wounding the mouth,) and with that make an incision in those gums which appear to cause the pain, always making it a point to feel the razor grate against the tooth, and then I am pretty sure it will advance without difficulty. I have often done this when the gums were very much swelled and inflamed, and the child in such distress as to require every exertion to keep it tolerably quiet: in half an hour afterwards the whole edge of the teeth where the incision was made have been visible, and in the course of a few hours, the inflammation has subsided, and the infant appeared surprisingly relieved. I always perform this simple operation as the infants lie asleep in my lap, nor do I recollect a single instance of their awaking from it.

THE MATERNAL PHYSICIAN, NEW YORK, 1811.

LOCAL TOLERANCE TO PENICILLIN

A Comparison of Five Intramuscular Preparations

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THE development of benzathine penicillin G has been an important milestone in antimicrobial therapy. One intramuscular injection of 600,000 units will usually provide detectable penicillin levels for ten to fourteen days; 1.2 million units will prolong the penicillinemia for four weeks. The efficacy of this preparation in the treatment and prophylaxis of group A hemolytic streptococcus infections has been well documented.[1-3] Monthly injections of benzathine penicillin G have been used effectively to prevent streptococcal infections in patients with rheumatic fever.[4]

The chief deterrent to the use of benzathine penicillin G in pediatric practice is the high incidence of local reactions. Severe, painful muscle soreness with limp develops frequently and persists for several days following inoculation. The poor local tolerance to this preparation has undoubtedly retarded its wider use.

This study was undertaken to compare the local tolerance to five penicillin preparations.

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Supported by a grant from Wyeth Laboratories, Inc., Philadelphia, Pa.

*The penicillin preparations were kindly supplied by Wyeth Laboratories, Inc.: (1) Bicillin 600 suspension; (2) Bicillin 600 suspension with 5 mg. cortisone; (3) Bicillin 600 suspension with 2 mg. of 9-alpha-fluoro-hydrocortisone alcohol; (4) Bicillin 600 C-R suspension; (5) Wycillin 600 suspension.

PLAN OF STUDY

The following five penicillin preparations* were evaluated:

1. Benzathine penicillin G suspension, 600,000 units in 1 c.c.
2. Benzathine penicillin G suspension with 5.0 mg. of cortisone, 600,000 units in 1 c.c.
3. Benzathine penicillin G suspension with 2.0 mg. of 9-alpha-fluorohydrocortisone alcohol, 600,000 units in 1 c.c.
4. Benzathine penicillin G, 300,000 units, plus aqueous procaine penicillin, 300,000 units, both in 1 c.c.
5. Aqueous crystalline procaine penicillin, 600,000 units in 1 c.c.

Each injection was given from a disposable unit (Tubex) identified by a code number. The study was conducted in the Bellevue Hospital outpatient department. The following criteria were set up for admission to the group: (1) there had to be an indication for penicillin therapy; (2) children under 3 years were to be excluded because of the difficulty in evaluating the younger age group; (3) only the initial injection of penicillin was to be evaluated.

The particular type of penicillin given to the patient was selected at random by the nurse who recorded the penicillin code number on a special card. All of the injections were given by experienced pediatric staff nurses. Each patient was given an appointment to return in twenty-four hours.

When the patient returned, he was seen by one of the authors (V. E. P.) who evaluated all of the children in the series and was unaware of the type of penicillin administered. The following observations were recorded on the card: (1) erythema; (2) induration; (3) tenderness; (4) muscle spasm (limp); (5) pain; and (6) other pertinent remarks. An attempt was made to obtain a follow-up at forty-eight hours also.

RESULTS

A total of 297 injections of the five penicillin suspensions was given to children whose ages ranged from 3 to 13 years; the average age was 6.7 years. Of these, thirty-three (11.1 per cent) did not return for follow-up and twenty (6.7 per cent) were disqualified because they did not fulfill the criteria set up for the study. A total of 244 injections (82.2 per cent) was evaluated.

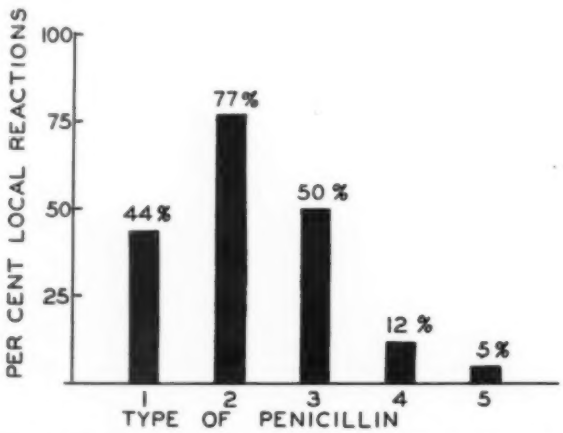

Fig. 1.—Comparative incidence of local reactions to five intramuscular penicillin suspensions. (*1*) Benzathine penicillin G suspension, 600,000 units in 1 c.c. (*2*) Benzathine penicillin G suspension, 600,000 units, plus 5 mg. cortisone, in 1 c.c. (*3*) Benzathine penicillin G suspension, 600,000 units, plus 2 mg. fluoro-hydrocortisone alcohol in 1 c.c. (*4*) Benzathine penicillin G, 300,000 units, plus aqueous procaine penicillin, 300,000 units, in 1 c.c. (*5*) Aqueous procaine penicillin, 600,000 units in 1 c.c.

The original plan of the study was to give 100 injections of each of the five preparations. However, after one-third of this number was given, it became apparent that a fairly large group of patients were returning with severe local reactions. It was apparent that these reactions were limited to three of the code numbers. Consequently, it was decided to discontinue any further investigation of these three preparations. The study was completed with the last two penicillin suspensions.

During the course of the study it became apparent that the most reliable objective criterion of local reaction was "limp." The severity of the limp was closely related to the severity of the induration, tenderness, and pain. These criteria were used as a basis for tabulating the incidence of local reactions shown in Table I and Fig. 1. The rate of local reactions was 5 per cent in the control group of patients who received 600,000 units of aqueous procaine penicillin. In the benzathine penicillin G group the rate

was 44 per cent; with 5 mg. of cortisone and 2 mg. of fluoro-hydrocortisone alcohol added, it was 77 per cent and 50 per cent, respectively. The combination of benzathine penicillin G and aqueous procaine penicillin produced 12 per cent local reactions.

Pain at the site of injection was the only untoward reaction noted in the 244 children in this study. No other side effects of penicillin therapy were observed.

TABLE I. COMPARISON OF LOCAL REACTION TO FIVE PENICILLIN SUSPENSIONS

PENICILLIN SUSPENSION*	NO. OF PATIENTS	AVERAGE AGE (YEARS)	LOCAL REACTIONS	
			NO.	PER CENT
1	32	7.5	14	44
2	31	6.7	24	77
3	26	7.2	13	50
4	77	6.5	9	12
5	78	6.4	4	5

*1. Benzathine penicillin G suspension 600,000 units in 1 c.c. 2. Same as 1, with 5.0 mg. of cortisone added. 3. Same as 1, with 2.0 mg. of 9-alpha-fluoro-hydrocortisone alcohol added. 4. Benzathine penicillin G, 300,000 units plus aqueous procaine penicillin, 300,000 units in 1 c.c. 5. Aqueous procaine penicillin suspension, 600,000 units in 1 c.c.

DISCUSSION

The addition of either 5 mg. of cortisone or 2 mg. of 9-alpha-fluorohydrocortisone alcohol to a suspension of 600,000 units of benzathine penicillin G did not improve the local tolerance to this preparation in this group of children. On the other hand, the addition of 300,000 units of aqueous procaine penicillin to 300,000 units of benzathine penicillin G did reduce the local reaction rate from an average of 44 to 12 per cent. The latter rate also compared favorably with the 5 per cent of local reactions that followed aqueous procaine penicillin alone.

Many of the children who received the mixture of aqueous procaine penicillin and benzathine penicillin G had pain for twelve hours following injection. However, when they were evaluated at twenty-four hours the local reaction had already subsided. Both the severity and duration of the muscle soreness was decreased with this preparation as compared to the suspension of benzathine penicillin G.

Breese and Disney[1] have shown that a single intramuscular injection of 600,000 units of benzathine penicillin G will cure group A hemolytic streptococcal infections promptly, and will prevent recurrences and complications in 94 per cent of patients. In their study a group of 100 children was followed for local reaction to the injection of benzathine penicillin G. According to mothers' reports there was soreness at the site of injection to a moderate or severe degree in 47 per cent of the children for a period of one to more than three days.

It should be emphasized that the combined aqueous procaine penicillin and benzathine penicillin G suspension contained only 300,000 units of the latter form of penicillin. There is no evidence to suggest that one intramuscular injection of this preparation in this dosage is adequate therapy for streptococcal infections. Accordingly, if this suspension were to be used, at least two injections should be given at five-day intervals.

At present we are evaluating a preparation which contains 600,000 units of aqueous procaine penicillin and 600,000 units of benzathine penicillin G in a 2 c.c. disposable syringe.* Preliminary observations indicate that this 2 c.c. combination dose causes less

*Wyeth Laboratories, Bicillin C-R 600.

local muscle soreness than does 1 c.c. of benzathine penicillin G, 600,000 units.

SUMMARY

Five types of penicillin for intramuscular injection were evaluated for intensity of local reaction: (1) benzathine penicillin G suspension, 600,000 units in 1 c.c.; (2) benzathine penicillin G suspension, 600,000 units, with 5 mg. of cortisone in 1 c.c.; (3) benzathine penicillin G suspension, 600,000 units, with 2 mg. of 9-alpha-fluoro-hydrocortisone alcohol in 1 c.c.; (4) benzathine penicillin G, 300,000, units plus aqueous procaine penicillin, 300,000 units in 1 c.c.; and (5) aqueous procaine penicillin, 600,000 units in 1 c.c.

A total of 244 children were evaluated at twenty-four hours after injection and the following percentages of local reaction were recorded for the five penicillin suspensions listed: (1) 44 per cent, (2) 77 per cent, (3) 50 per cent, (4) 12 per cent and (5) 5 per cent.

The addition of steroids to benzathine penicillin G did not alter the high rate of local muscle soreness in this group of children.

A mixture of 300,000 units of benzathine penicillin G and 300,000 units of aqueous procaine penicillin gave the lowest local reaction rate for both intensity and duration when compared with other repository preparations containing benzathine penicillin G. Although many of the children complained of pain for twelve hours following the injection of such a mixture, when evaluated at twenty-four hours most of the symptoms had subsided.

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TOXIC EFFECTS OF HALF-STRENGTH AMINOPHYLLINE SUPPOSITORIES IN ASTHMATIC CHILDREN

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EARLY in 1954 a letter appeared in the *Journal of the American Medical Association*[1] which reported alarming reactions in two asthmatic children following the use of rectal aminophylline. The first, a 3½-year-old child, went into severe shock one-half hour after the insertion of an aminophylline suppository, but responded to antishock treatment. The second patient, a 2-year-old child, had a similar reaction from which she did not recover.

Later reports by Frazier in the *J. A. M. A.*,[2] and by Rounds[3] and Love[4] in pediatric journals showed clearly that these were not isolated accidents due to singular effects in unusually sensitive children, but were the result of overdosage. Since physicians are usually cautious in prescribing the proper doses of the drugs they use in children, it seems astonishing that reports of such unusually severe toxic effect from a drug which has been in use for fifty years should appear in such widely separated areas (Massachusetts, North Carolina, California, Washington) in so short an interval.

Review of previous reports as well as of the circumstances involved in our own similar experiences warrants the statement that these therapeutic accidents are due to (1) the hazardous assumption that half-strength aminophylline suppositories which contain 250 mg. are suitable for small children and (2) the casual and too frequent repetition of a drug which, because of its unpredictable rate of absorption, induces cumulative effects.

From the Milwaukee Children's Hospital.

CASE REPORTS

CASE 1.—L. M. (Hosp. No. 85995), a 4-year-old asthmatic child, weighing 43 pounds, was brought to the outpatient department of the Children's Hospital on Nov. 9, 1954. For two days prior to the visit, the child had suffered from asthma, accompanied by diarrhea and vomiting. She had no bowel movement on the day of the visit. An aminophylline suppository, "child's size," containing 0.250 Gm., was prescribed and the child sent home. The following noon, acutely ill, with recurrent vomiting, dyspnea, slight fever, and complaining of abdominal pain, she was admitted to the hospital. Dyspnea was somewhat relieved by an injection of 1:1,000 Epinephrine solution. Parenteral penicillin was ordered, as well as aminophylline suppositories, 0.250 Gm., every 6 hours for four doses. During the ensuing twelve hours, she vomited all fluids taken. About fifteen hours after admission, she appeared bewildered, talked incoherently, had stiffness of the neck and back and a positive Kernig's sign. The heart rate was 240, blood pressure 110/65. Spinal tap revealed a negative globulin, total protein 10 mg. per cent, and glucose 77 mg. per cent. Blood sugar was 100 mg. per cent, nonprotein nitrogen

31 mg. per cent. X-ray of the long bones showed no lead lines. Electrocardiogram was normal. Electroencephalogram showed some 14 to 16 per second positive spikes in the temporal and occipital areas. By evening of the second day, following intravenous fluids and the completion of the battery of laboratory tests, she began to retain oral fluids and regained orientation. An unsteady gait remained for several days. She was discharged without symptoms on Nov. 15, 1954, after a second negative spinal fluid determination.

CASE 2.—G. W. (Hosp. No. 90904), a 20-month-old girl, had been previously hospitalized at the age of 7 months for asthmatic bronchitis. During her second year, she had at least nine episodes of asthmatic bronchitis following upper respiratory infections.

Four days prior to the last hospital admission she developed an upper respiratory infection and began wheezing after forty-eight hours. During the thirty-six-hour period before hospitalization, the mother had given the child a total of five 0.250 Gm. aminophylline suppositories. About twelve hours before entrance to the hospital, the child began to vomit and nine hours later began convulsing. She was seen at another hospital, and given sodium Luminal, aspirin, and oxygen with little improvement.

On admission to the Children's Hospital the child was still having a generalized convulsion, appeared toxic, dehydrated, and acidotic. She was unresponsive. Her chest was filled with coarse ronchi and wheezing. Spinal fluid examination showed 1 lymphocyte, 10 mg. per cent protein, 106 mg. per cent sugar. Calcium was 8.6 mg. per cent. Blood sugar was 45 mg. per cent. CO_2 combining power was 11.2 meq. per liter. Serum chloride was 92 meq. per liter. A blood pH was 7.05.

The child was treated with intravenous fluids, barbiturates, open-drop ether, antibiotics, and cortisone, but her condition deteriorated rapidly and she died five and one-half hours after admission. Post-mortem report (Dr. Claudon). Diagnosis: Subacute peribronchitis and peribronchiolitis. Toxic encephalopathy. Microscopic examination: Lungs revealed mixed inflammatory infiltrate about many of the bronchioles. Foci of intra-alveolar hemorrhage and collapsed alveoli were seen. Brain—some of the cerebral neurons showed early degenerative changes. There was considerable perivascular edema in the cerebellum. The anterior horn cells of the cord displayed karyorrhexis. Liver, spleen, and subcortex of kidneys appeared congested. Thymus, adrenals, pancreas, bone marrow, no significant lesions.

CASE 3.—J. M. (Hosp. No. 93734), a 4-year-old boy, weighing 34 pounds, was well until one week before hospitalization when he developed an upper respiratory infection. The morning of the day of admission he began wheezing, complained of epigastric distress, and vomited four times. When admitted to the hospital he was having moderate respiratory distress with a respiratory rate of 36 per minute and a temperature of 102.2° F. (R). Suprasternal retraction was present, ronchi and wheezes were heard throughout the entire chest. The child was placed in a humidified atmosphere, given Dicrysticin, iodides, and aminophylline suppositories, "child's size," ordered every six hours. The child's condition improved during the first twelve hours. He then began vomiting frequently. In spite of parenteral fluids, the emesis persisted. The child became dehydrated, began hyperventilating, and had a generalized convulsion. During a thirty-hour period he had received six 3¾-grain aminophylline suppositories.

The aminophylline was discontinued, but the child continued to remain very hyperactive and febrile (104° F.), and became disoriented. Urine showed a 1 plus albuminuria; CO_2 was 10.3 meq. per liter. An electrocardiogram showed a sinus tachy-

cardia of 187. Treatment consisted of the administration of large amounts of parenteral fluids, digitalization, parenteral penicillin, with gradual disappearance of the toxic symptoms.

One week after admission the child developed neck and hamstring spasm. A spinal fluid examination was normal. Four days later the child was discharged well.

CASE 4.—T. L. (Hosp. No. 94930), a 5-year-old boy, weighing 37 pounds, had a history of eczema and two episodes of asthma beginning at 3½ years of age. Five days prior to hospitalization he developed a fever, nonproductive cough, and asthmatic-type breathing. Two days before admission, during a twenty-four-hour period, he received a total of six suppositories, each containing 0.250 Gm. of aminophylline. He became restless, irrational, and began vomiting after the third suppository was administered. On admission to the hospital the child was very restless, markedly dehydrated, and vomiting. A CO_2 combining power was 13.9 meq. per liter and urine showed a trace of albumin. Treatment consisted of intravenous fluids, antibiotics and supportive measures. The patient improved and was discharged from the hospital four days later.

DISCUSSION

Side effects following excess dosage of aminophylline—gastric irritation with nausea, vomiting and diarrhea, tachycardia, and convulsive seizures—have been known since the earliest use of the drug. Occurring in a child, these symptoms may be mistakenly regarded as part of the picture of dehydration which may accompany the asthmatic attack, and not recognized as the warning sign of aminophylline intoxication. Depression of tubular reabsorption and acidosis may then create irreversible and alarming effects.

It may be well to recall the dosage as well as the frequency of administration employed by those who have had wide experience with aminophylline. We have reviewed the spate of publications which appeared during the ten-year period following Herrmann and Aynesworth's[5] first extensive report of the use of aminophylline in asthma. Since most of these publications deal with adults, the usual modifications need to be made in applying their data to children. Herrmann and Aynesworth include in their study a 13-year-old girl with status asthmaticus who obtained relief after an intravenous injection of 0.240 Gm. aminophylline. Several years later she returned in "status asthmaticus." Her condition was critical. Ten minutes after an intravenous injection of 0.120 Gm. aminophylline, she was able to breathe with comparative ease.

According to Hyman,[6] adult patients with severe asthma who sought relief during the night at the Atlantic City Hospital responded to a dose of 0.240 Gm. intravenously. Lamson and Bacon,[7] in a critical study of the proper dosage of aminophylline, found that thirty-six of forty-one adult patients obtained relief from a dose of 0.200 Gm. or less.

The majority of experienced allergists advocate an intravenous or rectal dose of 0.500 Gm. (7½ grains). Some suggest reducing this dose on first administration of the drug.

Frequency of Administration.—Most authorities agree that aminophylline given intravenously or rectally need not be given oftener than once every twelve to twenty-four hours. Rackemann[8] advised an injection on each of two or three evenings. Efron and Everett[9] found it unneces-

sary, even in the most severe cases, to give it more often than every twenty-four hours. Prickman and Gelbach[10] stated that suppositories may be used twice a day if required, and Susan Dees[11] suggests that "ordinarily, one suppository morning and evening is adequate."

The need for caution in repeating rectal doses of aminophylline is affirmed by the investigations of Waxler and Schack,[12] and of Jerzy Glass and his associates[13] who demonstrated persistent and appreciable blood levels after six hours, varying with (1) the vehicle used, (2) the local state of the rectum, and (3) the constitutional variations of the subject.

Comparison of Intravenous and Rectal Dosage.—While comparatively little is known about the relative doses and effects of drugs given rectally and intravenously, experienced pediatricians have long realized that the rectal mucosa provides an excellent absorption surface.

In the case of aminophylline, it has been amply demonstrated that, allowing for an initial delay in some patients, the bronchodilating effect of aminophylline given rectally is equal to that obtained after intravenous medication.[14]

Bearing this evidence in mind, the explanation for the severe toxic effects which occurred in these children is not far to seek. The most alarming reactions seen in our wards as well as witnessed by those who had previously called attention to the subject (including the recent report by Nolke*) were seen in children under 4 years of age. Four out of five have been 3 years or under. In our experience, severe asthma attacks necessitating hospital admission usually occur in this age group.

The dose of aminophylline for a 150 pound adult as used by the majority of allergists is 0.500 Gm. The dose for a child under age 3, weighing approximately 30 pounds, if computed on the basis of relative weight should not exceed one-fifth of the adult dose, or 0.100 Gm., instead of the 0.250 Gm. available in trade packages. The hazard of the higher dose is aggravated when the child has been given previous oral medication containing aminophylline as one of its ingredients, or has had successive rectal suppositories administered either by the mother or by a nurse following a p.r.n. order.

The unpleasant side effects of aminophylline and other xanthine drugs, whether given orally,[15] rectally, or intravenously, have been known since their introduction into medicine. These effects can be minimized by judicious modification of doses and methods of administration.[16] The easy availability of half-strength aminophylline suppositories, wrongly assumed to be a child's dose, has introduced a new and serious danger in the treatment of asthmatic children under 4 years of age.

We wish to thank Drs. Walter Polacheck, Reuben Snartemo, Eli Gecht, and Victor Kores for the privilege of reporting the cases from their medical services.

*This report appeared after our paper was written. J. A. M. A. **161**: 693, 1956.

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Pediatric Surgery, 1710

Advertisement

For the benefit of any that has or may have Occasion.

Henry Hill, Distiller in the Town of Boston New-England, having had a Child grievously afflicted with the Stone, apply'd himself to Mr Zabdiel Boylston of the said Boston Practitioner in Physick and Chirurgery: who on the 24th of June last, in presence of sundry Gentlemen, Physicians and Chyrurgeons, Cut the said Child, & took out of his Bladder a stone of considerable higness, and with the blessing of God in less tham a months time has perfectly Cured him, and holds his Water: This is his third Operation performed in the Stone on Males and Females, and all with good Success; He likewise pretends to all other Operations in Surgery. Which Operation the said Hill could not omit to make Publick.

BOSTON NEWS-LETTER, July 24, 1710.

THE EFFECT OF VINEGAR ON THE GROWTH OF ENTERIC BACTERIA IN EVAPORATED MILK MIXTURES

JAMES O. BOND, M.D., M.P.H.
JACKSONVILLE, FLA.

NEW interest in an old idea has recently been stimulated by the report of Seymour and associates[1] on the bactericidal effect of the addition of common vinegar to infant milk formulas. It will be the purpose of this paper to report the results of experiments on the growth of *Escherichia coli* and *Shigella flexneri* bacteria in acidified milk formulas and suggest the practical implications of these findings.

The history of the acidification of milk for infant feeding and the reasons proposed for it is a long and interesting one and is excellently reviewed in the report[1] mentioned above. In brief summary, buttermilk was the first acid milk mixture to be used in infant feeding, and its beneficial effect was held to be due to the low fat content as compared with sweet milk preparations. It was then shown that addition of acid to cows' milk decreased its buffering capacity on the gastric contents, restoring a more normal pH value and thus producing a presumed beneficial effect on the action of gastric enzymes. Various acids were proposed and widely used to achieve this effect, such as hydrochloric acid, citric acid from lemon and orange juice,[2] lactic acid, and vinegar.[3] Brennemann[4] in 1929 suggested that the ease of digestion of acidified milk was due largely to the production of a soft curd, and the use of lactic acid milks for this purpose in the ensuing years enjoyed a wide practice in the United States. Evaporated milk with its ability to achieve this same effect has, in recent years, largely replaced the use of acidified milks, and the rationale for use of the latter has been less apparent. However, the above-cited report on the bactericidal effect of acidified milk mixtures, confirming and extending the earlier reports of Rothey[5] and Taylor and Roberts,[6] is of practical importance for groups in our population which do not have adequate refrigeration, and suggested a need for further examination of the problem.

The bactericidal effect of vinegar is held to be due to its acetic acid content which, in common commercial preparations, ranges from 4 to 6 per cent. The effect of acetic acid and acetate ions on the growth of various microorganisms has been the subject of a number of papers over the past few years.[11-13] A summary of those findings indicates that the acetate ion and the undissociated acetic acid exert a specific toxic inhibitory effect on the growth of various bacteria and, more

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particularly, the gram-negative bacteria. In general, it is inhibitory at higher dilutions than other organic acids, and at lower hydrogen ion concentrations than those at which strong mineral acids are inhibitory to growth. While the mechanism of this action is unknown, it is generally agreed that it is not due to the hydrogen ion concentration alone, since the acetate ion and undissociated acid appear to play a specific role.

EXPERIMENTAL METHODS

The general experimental approach used was a determination of the growth curves of the selected bacteria over a twenty-four-hour period, in the unmodified and in the acidified evaporated milk mixtures. Stock cultures of *Esch. coli*, B/r strain, or *S. flexneri* were transferred from cystine trypticase agar (C.T.A.) tubes to 100 ml. flasks of trypticase infusion broth and incubated for eighteen to twenty-four hours at 37° C. Inocula of 1 or 2 ml. of 1:10,000 dilutions of these broth cultures were made in 100 ml. of the milk media under study, giving an initial concentration of 300 to 600 organisms per milliliter of medium.

These inoculated milk samples were incubated at 37° C., except where noted, and estimations of the numbers of organisms present at one- or two-hour intervals for the first eight hours, then at twelve and twenty-four hours were made by standard quantitative plating techniques using three or five replicates at each dilution. *Esch. coli* was plated on endo agar and *S. flexneri* on trypticase-soy agar, the plates incubated for forty-eight hours at 37° C., and the number of visible colonies counted at the end of this time in a Buck Colony Counter. Arithmetic means of the three or five replicates multiplied by dilution factors were taken as the final estimate of the numbers of bacteria present at each given interval.

The basic evaporated milk formula was that described by Seymour and coworkers,[1] consisting of 40 per cent evaporated milk, 3 per cent added carbohydrate in the form of commercial corn syrup, and 57 per cent water (corresponding to 13 ounces of evaporated milk, 17 ounces of water, and 2 tablespoons of sugar). The acidified milk was prepared by the addition of 4 per cent vinegar to the basic formula, with the appropriate reduction in water. Vinegar was purchased at local retail stores, as were also the evaporated milk and corn syrup. Studies for sterility of each product were made, and the vinegar was assayed for its acetic acid content according to the methods of the Association of Official Agricultural Chemists.[7] A close conformity of acetic acid content to that printed on the label (4 to 5 per cent) was found for each of four different brands. It was also found that storage of the commercial bottle over a three-month interval resulted in a slight increase in the acidity, presumably due to water evaporation (5.12 to 5.35 per cent).

For each experimental set of growth curves, single species of bacteria were grown simultaneously in the plain and the acidified milk formulas. Determinations of pH values of each culture were made with a Beckman potentiometer at zero, six, twelve, and twenty-four hours of growth.

RESULTS OF INVESTIGATIONS

Standard Error of the Method.—Determinations for the standard error

of the method were made with *Esch. coli* in the unmodified milk formula, grown at 37° C. These results are shown in Table I and Fig. 1. It is seen that the limits of the mean, plus or minus two standard errors, were relatively narrow as plotted on log paper, and deviations from this samples were within a narrow range indicates a minimum of sampling error.

The numerical growth of *Esch. coli* in the plain and vinegar milk is shown in Fig. 2, as plotted on semilog paper, which, it should be remembered, shows rates of growth and never reaches zero.

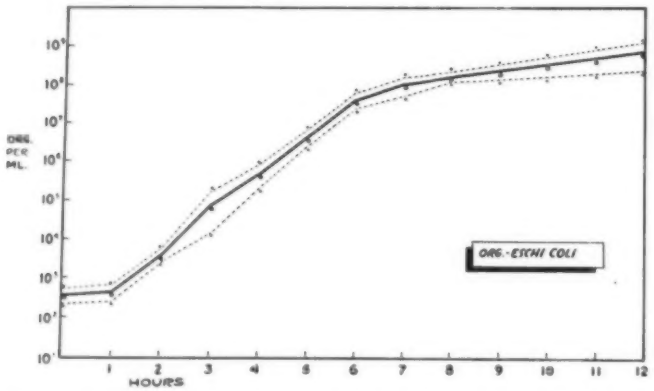

Fig. 1.—Growth of *Esch. coli* in evaporated milk formula at 37° C. Plotted on semilog scale.

TABLE I. GROWTH CURVE FOR ESCHERICHIA COLI IN AN EVAPORATED MILK MEDIUM
(Estimated Mean Number of Organisms per Milliliter by Hourly Intervals; the Standard Error of the Estimate, and of the Mean)

HOUR	MEAN COLONY COUNT × DILUTION FACTOR	STANDARD ERROR OF ESTIMATE	MEAN, PLUS OR MINUS 2 STANDARD ERRORS	STANDARD ERROR OF MEAN
0	37.4×10^1	6.27×10^1	$24.8\text{-}50 \times 10^1$	2.6×10^1
1	53.6×10^1	11.7×10^1	$30.2\text{-}77 \times 10^1$	5.2×10^1
2	45×10^2	8.47×10^2	$27.2\text{-}62.8 \times 10^2$	4×10^2
3	88.2×10^3	37.8×10^3	$12.6\text{-}164.8 \times 10^3$	16.9×10^3
4	69.6×10^4	14.3×10^4	$21.0\text{-}78 \times 10^4$	6.4×10^4
5	42.6×10^5	8.8×10^5	$25.0\text{-}60.2 \times 10^5$	3.9×10^5
6	31.2×10^6	3.5×10^6	$24.2\text{-}38.2 \times 10^6$	1.5×10^6
7	107.0×10^6	24.1×10^6	$58.8\text{-}155.2 \times 10^6$	10.8×10^6
8	184.8×10^6	21.1×10^6	$142.6\text{-}227.0 \times 10^6$	9.4×10^6
12	72.6×10^7	26.1×10^7	$20.4\text{-}124.8 \times 10^7$	11.7×10^7

growth pattern, later found in the acidified milk, were of a magnitude not likely to be produced by chance alone. The fact that consecutive curves of growth in the unmodified milk in our studies showed almost identical patterns and the estimated number of bacteria in the zero-hour

The addition of 4 per cent vinegar, which contained 5.6 per cent acetic acid, giving a final concentration of 0.224 per cent acetic acid (0.037 molar), completely inhibited the growth of *Esch. coli*. There was a slight bactericidal effect, with a constant death rate of approximately 10 per cent per

hour, so that by the twenty-fourth hour the medium was in effect sterilized.

Shigella Flexneri Growth Curves.—The numerical growth of *S. flexneri* in the plain and acid milk media is shown graphically in Fig. 3. The preceding studies were done with a uniform milk incubation temperature of 37° C., since this was the temperature used by previous investigators whose work we were attempting to confirm. However, in actual practice milk for infant feeding would rarely,

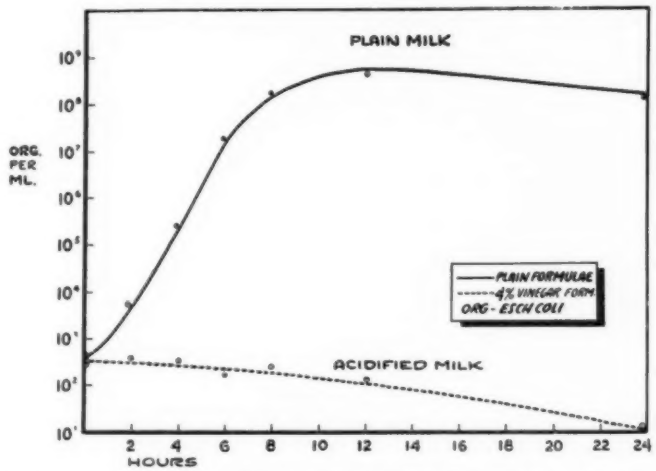

Fig. 2.—Growth of *Esch. coli* in unmodified and acidified evaporated milk formulas at 37° C. Plotted on semilog scale.

TABLE II. ARITHMETIC MEAN OF PLATE COUNTS OF ESCH. COLI GROWTH IN PLAIN AND ACIDIFIED MILK

	EVAPORATED MILK MEDIA			
	UNMODIFIED		ACIDIFIED	
HOUR	pH	BACTERIA/ML.	pH	BACTERIA/ML.
0	6.2	4.3×10^2	4.9	3.5×10^2
2		5.3×10^3		3.2×10^2
4		2.8×10^5		2.7×10^2
6	6.0	2.4×10^7	4.8	1.9×10^2
8		1.4×10^8		2.1×10^2
12	4.9	6.0×10^8	4.8	1.0×10^2
24	4.6	2.7×10^8	4.7	none to 10

vinegar added had a concentration of 5.35 per cent acetic acid, giving a final concentration of 0.214 per cent acetic acid (0.035 molar). The bactericidal effect of this added acid is more marked than in the case of *Esch. coli*, with practical sterilization of the media accomplished by the sixth hour.

Relationship of Incubation Temperatures to Acid Inhibition.—The if ever, be held at this temperature and it might therefore be useful to know how different incubation temperatures would influence this effect of the acetic acid.

Accordingly, the standard acidified formula, as previously described, and the unmodified control milk media were inoculated with another stock culture of *S. flexneri*. After obtain-

ing the zero hour, quantitative plate counts, the respective media were divided into three aliquots. These aliquots were incubated at 37°, 20°, and the organisms grew in the plain milk. The other experimental temperature, 4° C., is, of course, below the range in which this organism grows.

TABLE III. ARITHMETIC MEAN OF PLATE COUNTS OF S. FLEXNERI GROWTH IN PLAIN AND ACIDIFIED MILK

	EVAPORATED MILK MEDIA			
	UNMODIFIED		ACIDIFIED	
HOUR	pH	BACTERIA/ML.	pH	BACTERIA/ML.
0	6.3	4.4×10^2	5.1	5.8×10^2
2		3.7×10^3		4.8×10^2
4		1.2×10^5		1.1×10^2
6	6.3	3.3×10^6	5.1	none
8		3.8×10^7		none
12	5.8	1.4×10^8	4.9	none
24	5.5	1.6×10^8	4.9	none

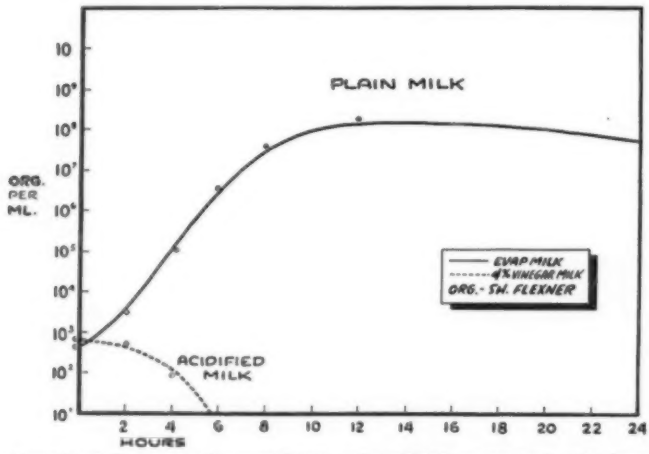

FIG. 3.—Growth of *S. flexneri* in unmodified and acidified evaporated milk formulas at 37° C. Plotted on semilog scale.

TABLE IV. ARITHMETIC MEAN OF PLATE COUNTS OF S. FLEXNERI GROWTH IN PLAIN AND ACIDIFIED MILK AT 4°, 20°, AND 37° C.

HOUR	PLAIN			ACIDIFIED		
	37°	20°	4°	37°	20°	4°
0	1112	1112	1112	1524	1524	1524
6	48×10^6	61×10^2	1526	1836	1450	1608

4° C. After six hours quantitative plate counts were again made, using five replicates for each determination. The results are given in Table IV.

These results indicate that the acidified milk has a bacteriostatic effect at 20° and 37° C., at which temperatures

It is of considerable interest that the vinegar milk did not have a bactericidal effect at 37° C. as in the previous experiment, but only a bacteriostatic one. All conditions were the same except the source of the *S. flexneri*, which in the second experiment

was from a different stock culture. This would seem to indicate a variation in susceptibility to the effects of acetic acid, within the species.

DISCUSSION

The results of the foregoing experiments confirm the previous findings that vinegar in 4 per cent concentration in milk has an inhibitory effect on the growth of *Esch. coli* and *S. flexneri*. This has been shown to occur at both 37° and 20° C. for *S. flexneri*. Since temperatures of 4° C. alone are bacteriostatic, it is evident that its main usefulnes would be as a substitute for refrigeration where this is not available. Its safety, cheapness, palatability, and availability appear to recommend it for this purpose over other chemicals, such as lactic acid and antibiotics.

There are many places in the world where the population is without adequate means of refrigeration and these findings might be of practical use, provided, of course, that milk is or can be made available. In the United States, where evaporated milk is widely used in preparing infant formulas in all economic groups, as a whole there are relatively few people who are without access to some type of refrigeration.

Table V shows that for the total United States, 9 per cent of the dwellings are without ice or mechanical refrigeration. However, it can also be seen from this table that access to refrigeration is not uniformly distributed throughout the population. Those living in rural areas, in the South and the Northwest, were less favored than their neighbors in 1950 in respect to availability of refrigeration. Physicians responsible for the care of infants in these regions and groups should perhaps be alerted to the necessity of making inquiry concerning the availability of refrigeration when prescribing a formula, since acidified milk might be considered as a possible substitute.

There are certain segments of the population wherein this lack of refrigeration is acute, and the substitution of vinegar milk might prove to be a significant addition to public health

TABLE V.* DWELLINGS IN UNITED STATES, 1950, REPORTED WITHOUT ICE OR MECHANICAL REFRIGERATION, BY REGION AND TEN HIGHEST STATES

STATES OR REGIONS	DWELLINGS SURVEYED	DWELLINGS WITHOUT ICE OR MECHANICAL REFRIGERATION	
		NUMBER	PER CENT
United States	42,059,850	3,894,265	9.0
Northeast	10,998,570	366,010	3.3
North Central	12,763,900	1,070,095	8.3
South	12,407,925	1,859,035	15.0
West	5,889,455	599,095	10.3
North Dakota	159,980	48,240	30.0
New Mexico	172,730	48,235	28.0
Mississippi	545,150	152,580	28.0
South Dakota	180,225	41,120	22.8
Kentucky	765,065	173,830	22.6
Alabama	773,100	169,655	22.0
West Virginia	510,740	108,775	21.2
Arkansas	515,010	106,755	20.6
South Carolina	506,600	100,000	19.8
North Carolina	976,335	190,870	19.5

*From 1950 U. S. Census of Housing, U. S. Summary, Vol. HA1, Table 20.

measures. The migrant labor group is perhaps the most outstanding example. There are estimated to be over 1,000,000 of these migrant farm laborers each year with an average family size of 5.7 persons. More often than not the entire family participates in the migration. Rates among them for epidemic and diarrheal diseases and infant mortality are reported as twice those in similar, nonmigrating populations.[8] Watt and associates[9] found the prevalence of Shigella-positive rectal swabs from children in these camps in one area to be fifteen to thirty times that found among the near-by permanent residents, and correlated this directly with the poor sanitation in the camps, especially lack of running water. Lack of refrigeration is also cited as a cause of these high rates of diarrheal disease and it has been found that 90 per cent of the camps in one state were without refrigeration facilities.[10] We feel that the introduction of vinegar milk formulas for infants in groups such as these would afford a significant contribution toward the improvement of their health.

As has been stated previously, it is generally agreed that the acetate ion or the undissociated acetic acid exerts a specific toxic inhibitory effect partially or completely independent of the effect of the hydrogen ion concentration. The nature of this action is unknown at present. Possible theoretical considerations are (1) it is a simple chemical combination with protein enzymes with irreversible denaturation, or (2) it belongs in the class of antimetabolite competitive inhibition mechanisms. There is some evidence in favor of the latter, since Dubos[16] has shown that alpha ketoglutarate partially reverses the inhibiting effect of acetate on the growth of tubercle bacilli and staphylococci.

Further studies along these lines would perhaps elucidate more clearly the metabolic pathways of the enteric bacteria and this precise knowledge should in turn lead to more effective methods of the control of their associated diseases.

SUMMARY AND CONCLUSIONS

By a study of growth curves of bacteria in plain and acidified evaporated milk mixtures, further evidence has been presented that the addition of 4 per cent vinegar produces an inhibitory effect on the growth of *Esch. coli* and *S. flexneri* at 37° and 20° C.

It has been concluded that this is due to a specific action of the acetic acid content of the vinegar, ranging from 0.214 to 0.224 per cent total concentration in the final mixture. The possible mechanisms of this effect have been discussed.

The practical usefulness of vinegar-modified infant feeding mixtures is suggested as being limited to a substitution for refrigeration where this is not available. In the United States its need and usefulness would probably be greatest in the migrant labor camps.

I wish to express my appreciation to Dr. Paul Harper and Dr. Robert C. Millonig for advice and assistance in carrying out this study.

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Early Signs of Measles

From An Account of the Measles, as it appeared in Berwick, County of York, Maine, 1802 and 1803. By Richard Hazeltine.

I notice no phenomenon which I could call a precursor of the disease, except the early appearance of the eruption in the internal fauces might be called one. In almost every instance where the commencement of the disease came to my knowledge, this appearance was to be observed at least 36, and in some cases 48 hours before the eruption appeared externally. I suspect the coryza, raucedo and tussis, which generally precede the cuticular eruption, and which constitute so important a trait in the diagnosis of the disease, are wholly attributable to this early eruption on the mucous membranes of the internal fauces, larynx, trachea, &c. I was informed by some persons, that they had pretty constantly observed a pale miliary eruption on the gums two or three days previous to the cuticular eruption; and I think I saw a case or two of this kind myself.

MEDICAL REPOSITORY. New York, 1804.

A COMPARATIVE STUDY OF A BANANA CARBOHYDRATE PROTEIN MILK VERSUS SKIM MILK IN THE CONVALESCENT DIARRHEA PATIENT

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HOUSTON, TEXAS

SKIM milk has long been accepted as a satisfactory first food for the infant and child during the period of convalescence from diarrhea. The low fat, relatively high protein content of this preparation is traditionally believed to be better tolerated by the recently disturbed gastrointestinal tract. For many years banana carbohydrate has occupied a place in the treatment of the celiac syndrome and related diarrheal states. In an effort to combine the virtues of these two preparations a high protein milk with banana carbohydrate has been placed on the market. This milk is described in Table I as banana carbohydrate protein milk. The composition of whole milk and skim milk are shown for comparison. The present study was conducted to compare the relative values to the banana carbohydrate protein milk and skim milk as first foods for infants and children convalescing from diarrhea.

TABLE I. PER CENT COMPOSITION NORMAL DILUTION

	PROT.	CHO	FAT	MIN.	CAL./OZ.
Probana*	4.0	7.6	2.1	0.6	19
Starlac†	3.5	4.9	0.1	0.7	11
Milk	3.2	4.5	3.3	0.7	18

*Mead Johnson and Co.
†Borden's nonfat dry milk.

From Department of Pediatrics, Baylor University College of Medicine, and the Pediatric Outpatient Clinic of Jefferson Davis Hospital.

Supported by a grant from Mead Johnson and Co.

The banana carbohydrate protein milk was supplied as Probana by Mead Johnson and Co.

MATERIAL AND METHODS

This study was conducted in the pediatric outpatient department of Jefferson Davis Hospital in Houston, Texas. The agents used were banana carbohydrate protein milk and skim milk. The study was carried out as follows: One hundred five children with diarrhea were selected from the general clinic population, and

1. All children were seen by one examiner.

2. Weights were measured on the same scale with the children nude.

3. Where antibiotic therapy was indicated by the patient's disease, Chloromycetin was used.

4. Consecutive patients were assigned alternately to banana carbohydrate protein milk or skim milk without respect to age or seriousness of their diarrhea.

5. Stool cultures were taken in random fashion in one out of five cases.

6. The treament regimen as planned is outlined as follows:

a. First 24 hours: salt and sugar water (½ teaspoonful of salt and 2 tablespoonfuls of sucrose in one quart of water) carbonated beverages or tea in ad lib quantities.

b. Second 24 hours: banana carbohydrate protein milk or skim milk on basis of prior selection.

c. Third 24 hours: to normal pre-diarrhea feeding schedules.

7. In many instances individual treatment periods were prolonged beyond that duration anticipated in the initial planning.

A record was kept which included the following information: number of stools, character of stools, color of stools, nude weight of child, number of days before normal diet resumed, acceptance of formula, regurgitation, and associated illness.

Although 105 children were included in this study, complete data are available on only 90 per cent. The major findings are tabulated in Table II.

That some idea may be gained as to the types of diarrheas studied, a tabu-

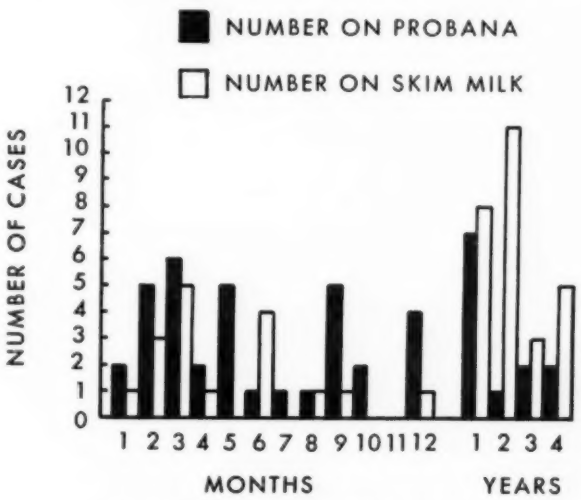

Fig. 1.—Age distribution of study patients.

TABLE II. SUMMARY OF COURSE OF NINETY INFANTS AND CHILDREN TREATED WITH PROBANA OR SKIM MILK IN DIARRHEA CONVALESCENCE

	PROBANA	SKIM MILK
Days to normal diet		
Average	3.4	3.5
Range	(2-5)	(2-9)
Gain in weight (oz.)		
Average	10	8.6
Range	(1-28½)	(½-23½)
Losing weight		
Number	3	6
Weight loss (oz.)		
Average	6.1	7
Range	(2½-8)	(4-16)
No change in weight		
Number	2	1
Patients hospitalized due to therapeutic failure	0	5
Patients refusing formula	10	3

TABLE III. BACTERIOLOGICAL FINDINGS OF THE TWENTY-THREE INFANTS WITH DIARRHEA CULTURED IN THIS STUDY

No pathogens	8
Proteus	2
Proteus and *Escherichia coli*	1
Shigella sera type B	1
Alcaligenes	1
Pseudomonas aeruginosa	2
Paracolobactrum	3
Proteus, alpha hemolytic streptococcus, and beta hemolytic streptococcus	1
Proteus, diptheroids, and *Esch. coli*	1
Proteus and alpha streptococcus	2 (twins)
Esch. coli, Staph. albus, diphtheroid, and *Klebsiella pneumoniae* (Infant had been treated the previous week with Aureomycin)	1

lated report on the stool cultures is included in this report (Table III).

Included in the report is a graph (Fig. 1) which demonstrates the age distribution of the two agents. Patients were assigned alternately to the two formulas without using ages as a determining factor.

DISCUSSION

This study demonstrated that the banana carbohydrate protein milk is a satisfactory first food for an infant or child recovering from diarrhea. There was a slightly greater weight gain when this milk was used. This is probably explained by the greater calorie content per ounce as compared to skim milk.

There were ten children in the study who refused the banana carbohydrate protein milk. They ranged from age 5 months to 3 years. Five of the children refused the formula completely while the other five took small amounts. In each case the formula was prepared correctly but the child objected to the taste. The objectionable taste is believed to be due to the casein hydrolysate.

No patients in the banana carbohydrate protein milk group were hospitalized, whereas five in the skim milk group were hospitalized. A complete explanation for this is lacking; however, two of the five hospitalized children developed complicating additional illnesses during their course of treatment for diarrhea, both having pyogenic abscesses of the subcutaneous tissue.

CONCLUSIONS

A study was undertaken to evaluate the relative value of the banana carbohydrate protein milk and skim milk as a first food in the infant or child convalescing from diarrhea. The data from ninety cases was analyzed. Fifteen additional cases were excluded from analysis because of incomplete data.

While the number of cases studied is too small to allow valid conclusions, the following points are of interest.

1. There was found to be no appreciable difference in the length of convalescence with the two agents.

2. Patients receiving the banana carbohydrate protein milk showed a slightly better weight gain.

3. More patients disliked the taste of the banana carbohydrate protein milk than skim milk.

POLYOSTOTIC FIBROUS DYSPLASIA (WITH PRECOCIOUS PUBERTY AND PIGMENTATION)

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IN 1922 Weil[1] described a 9-year-old girl who had the sexual and skeletal development of a 15-year-old child. She had menstruated since infancy and had had seven spontaneous fractures. She also had scattered pigmentation of the skin. In 1932 Freedman[2] reported a 6-month-old female infant with a celiac syndrome and vaginal bleeding. This infant had a large clitoris, measuring 1 cm., and hypertrophy of the labia. She had a brown pigmentation of the skin of the face and the back of the left leg and buttock. In Freedman's discussion he suggested as a cause, "possibly in the anterior lobe of the pituitary gland." In the same year, Gaupp[3] reported two cases of precocious puberty: one 8-year-old child who had enlargement of the breasts, pubic hair beginning at 3 years, but with no pigmentation of the skin, and one 9-year-old girl who started to menstruate at nine years. In the following year, Goldhamer[4] reported a case of precocious puberty with unilateral pigmentation of the skin. In the same year, Stalmann[5] reported an 8-year-old female who had unilateral pigmentation of the skin and osteitis fibrosa, who started to menstruate when she was 9 months of age. Albright and colleagues[6] reported a syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and endocrine dysfunction with precocious puberty in females. In April, 1937, seven patients were described and a subsequent paper was published in 1938. By this time the syndrome became known as Albright's syndrome. In 1947 Albright reviewed the literature extensively and presented sound arguments in favor of a definite entity, separate and distinct from any other, particularly from lipoid granulomatosis and neurofibromatosis. In his summary Albright[7] states: "1. This paper concerns the syndrome, which in its complete form is characterized by (1) a disseminated osteitis fibrosa (both hyper- and hypo-ostotic) with a segmental distribution, (2) areas of cutaneous pigmentation which have a distribution suggesting some connection between them and the bone lesions, and (3) sexual and somatic precocity when the condition occurs in the female." In 1937 McCune and Bruch[8] described a girl with osteodystrophia fibrosa, who started to menstruate at 2 years of age, when her breasts enlarged and she developed axillary and pubic hair. She had extensive marked bone changes. Sternberg and Joseph[9] reported the post-mortem findings on this child. They described a hyperplastic thyroid, thymus, and lymphatics. They also found mature cystic ovaries, with no evidence of luteiniza-

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tion, a narrow "lean" adrenal cortex, and parathyroids within normal limits. The pituitary showed basophilic hyperplasia with adenoma formation. Additional literature is reviewed.[10]

It is my desire to report a case of isosexual precocious puberty in a child 7 years of age, who has been followed and studied for six and one-half years. It will be noted in the history that this child had the earliest onset of any of the known cases reported, namely, at one month. The bone changes came late and so far are minimal.

CASE REPORT

A 5-month-old female infant born on Feb. 13, 1949, was seen in my office Aug. 2, 1949, because of a bloody vaginal discharge for two days. She was a first pregnancy, born after an 8½-month term, weighing 5 pounds 14 ounces. It was reported that there had been a mucous, odorless discharge for the past six weeks. The mother was a nurse, the father a physician. Some breast enlargement was noted at 1 month of age. Some pubic hair was seen the day before admission. On the first examination the infant weighed 16 pounds 4 ounces and measured 26½ inches in length. The anterior fontanel was open and measured 3 by 4 cm. The nutrition was good; mental response, good. On examination, multiple tan pigmented spots were noted on the back of the right chest, the right shoulder, and on the right arm and forearm. There was a pigmented areola around the nipples and a slight hypertrophy of both breasts. There was some hypertrophy of the labia majora and a small amount of fine pubic hair. On rectal examination, a small, soft uterus could be just palpated. The blood count, coagulation and bleeding time were normal. X-rays of the wrists showed a normal bone age and maturation. The infant was referred to the Mayo Clinic for studies of the estrogen and ketosteroid determinations. The following report was obtained:

"She is a well-developed little girl, has appeared mentally alert. There was an irregular light brown pigmented area on the back, on the right arm and on the left leg. There was a slight enlargement of the breast tissue beneath the nipples and very questionable increase in the pubic hair, and a serosanguineous vaginal discharge.

"The laboratory reports including blood count, urinalysis, were normal. The serum phosphate was 6.1 mg. per cent. The alkaline phosphatase was 9.9 units, the serum calcium was 10.1 mg. per cent. The twenty-four-hour specimen for 17-ketosteroids was negative for twenty-four hours. Vaginal smears showed both gram-positive and gram-negative organisms, red blood cells, epithelial cells, and no pus cells. The x-ray of the chest was negative. A flat plate of the abdomen showed no abnormality. The long bones showed fraying of the diaphysis distal end of the radius and ulna bilaterally and the tibias and fibulas. This may be due to the abnormality of growth associated with the sexual precocity. No definite evidence of accelerated bone development and no evidence of Albright's disease was noted. The appearance suggests rickets and this should be presumed until proved otherwise. We asked the gynecologist to see the child as none of us could feel an abdominal tumor by rectal examination. Urethroscopic examination of the vagina was done and showed no foreign body, the cervix was clear and normal, and vaginal mucosa was small. We did not feel that the uterus was exceptionally large for the age, and no masses were felt in the adnexa. The estrogen determination was normal. We did not feel that we were dealing with a tumor of the ovary, and felt inclined to recommend observation of the child for the present time. Should the signs of the sexual precocity become more marked, further observation would certainly be indicated."

The child was seen again in my office Sept. 13, 1949, when she weighed 17 pounds 15 ounces and measured 27 inches. There was a report of no further vaginal discharge. The phys-

Fig. 1.—Patient at 10 months of age (March 13, 1950), showing enlargement of breasts and nipples, with pigmentation on right shoulder, right forearm, and right chest.

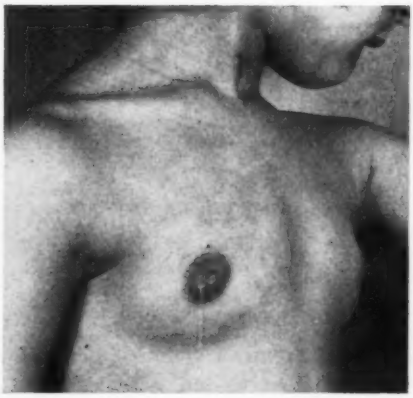

Fig. 2.—Patient at 4 years of age (May 14, 1953), showing marked enlargment of breasts and pigmentation of nipples and areolae.

Fig. 3.—Four years of age, showing hypertrophy of labia minora and majora.

Fig. 4.—Seven years of age, showing same pigmentation on right shoulder and marked enlargement of the breasts.

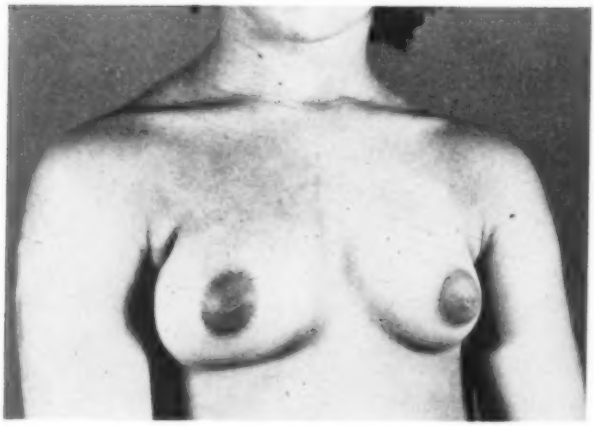

Fig. 5.—Seven years of age, showing marked hypertrophy of breasts and nipples.

Fig. 6.—Showing pubic hair and hypertrophy of the labia.

Fig. 7.—Tumor of right ovary, showing several cysts.

ical findings were about the same. On Dec. 23, 1949, she weighed 20 pounds 14 ounces and measured 29 inches. There had still been no further vaginal discharge. At that time there was no hypertrophy of the breasts. The anterior fontanel measured 2 by 2 cm. and there were six deciduous teeth. The skin discoloration had spread to the lumbar region. On March 13, 1950, the child was admitted to the Milwaukee Children's Hospital, where vaginal smears showed estrogen stimulation, not progestin. X-rays of the bones were reported negative or normal except for the epiphyses in the wrist, which showed a bone age of twenty-four months. A twenty-four-hour urine specimen showed no follicle-stimulating hormone. On April 1 a 17-ketosteroids was reported as 0.588 mg. On March 31, 1950, there was a recurrence of the enlargement of the breasts. At this time there was an increase in the pubic hair and hair was also found in the axillae and some on the upper lip. The skin was darker in color. The child had been discharged from the hospital but she was readmitted on March 31, 1950. Dr. Philip Seefeldt did an abdominal exploratory operation on April 3, 1950. At that time the uterus appeared to be enlarged and soft but not spongy. The right ovary was enlarged and contained one cyst, which measured 2 cm. in diameter and contained clear fluid and a small cyst, which measured 0.5 cm. in diameter. The left ovary appeared to be normal but a small section was removed for biopsy. This specimen showed several immature follicles and one round growth about five times the size of a normal follicle composed of cells of two types. Some of these cells were small, with darkly staining nuclei. Several rounded vacuoles were present here also. These were about the size of the larger type of cell and had rather ragged borders. Diagnosis was normal ovarian tissue.

The cyst was removed from the right ovary. On microscopic examination, the wall of the cyst was made up of ovarian tissue in which there were large numbers of immature follicles, most of which had apparently undergone degeneration and atresia. The lining of the cyst varied. In some areas it appeared to be made up of flattened cells with ovarian parenchyma immediately adjacent. In others there were granulosa cells in the lining and these were mixed with large vacuolated cells having the appearance of theca cells. The papillary upgrowth described grossly was composed of ovarian tissue, partially hemorrhagic, in the middle portion of which there were a large number of granulosa cells. This protrusion, however, was microscopic in size, being smaller than a low-power field. In the parenchyma there were, besides the atretic follicles, several enlarged follicles containing many granulosa cells. There was no further vaginal discharge until Dec. 9, 1950, when a brown fluid was noticed. This became creamy in color. The nipples were then slightly enlarged. The areolae around the nipples were larger and there was a further enlargement with some hair on the vulva. At this time an unusual reddish brown rosette about 2 cm. in diameter was noted at the lower fornix. Rectal examination revealed a uterus about pencil thickness and about 7 cm. long. The vaginal smear showed a uniform cell picture with precornified cells of the adult type of epithelium. All cells were broad but also all were nucleated. They took an acid stain and they appeared to be in a follicular phase. On Dec. 23, 1950, there was still a continued cream-colored vaginal discharge. There was some development of the nipples, of the areola, and there were definite small pads palpated under the nipples. There was an increase in pubic hair and the same rosette was observed. On April 23, 1951, there was no further vaginal discharge. The skin pigmentation remained the same as did the enlargement of the breasts, nipples, and areolae. The axillary

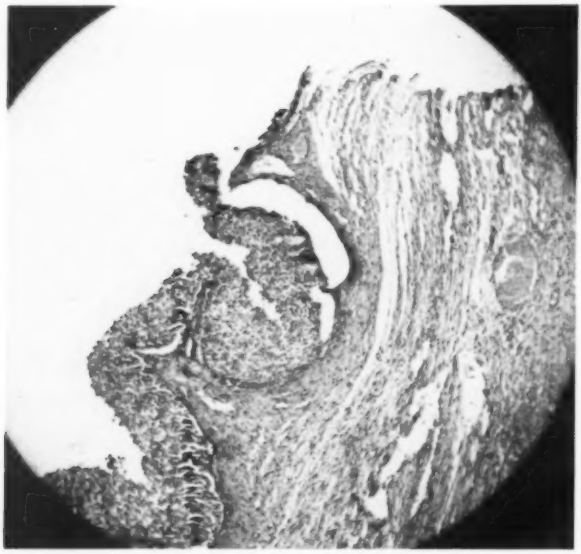

Fig. 8.—Photomicrograph of cystic ovary: the luteal-like cells many layers thick, line the cyst and rest upon a zone of compressed connective tissue.

Fig. 9.—Photomicrograph of endometrium made of spiral glands of secretory type in edematous stroma, with areas of decidual-like reaction.

and pubic hair were the same. On rectal examination, the uterus appeared to be of about the same size and consistency.

On May 25, 1951, it was reported that the child had fainted before breakfast one morning. The fasting blood sugar was normal and a sugar tolerance test was normal. On Aug. 9, 1951, it was reported that there had been no more fainting spells. There had been an occasional slight vaginal discharge. The blood pressure was 88/68. The areas of pigmentation in the skin were darker. The pubic hair had disappeared.

Fig. 10.—X-ray of skull, showing increased calcification of the base.

There was only a slight engorgement of the breasts and some pigmentation of the nipples. Abdominal and rectal examinations were negative. On Oct. 1, 1951, the child weighed 23½ pounds and measured 37⅛ inches. She had a slight pink-tinged vaginal discharge. There were more pigmentation in the skin areas and a slight increase in the size of the nipples and areola. A vaginal smear showed the entire material made up of superficial squamous cells, most of which contained small pyknotic nuclei about 20 per cent luteinized. The cells were considered to be normal for this age. On Dec. 29, 1951, the child weighed 36 pounds and measured 38¾ inches. There was some yellowish vaginal discharge. The pigmentation was the same. Blood pressure was 90/60.

The child was next examined May 7, 1953, at which time she weighed 47½ pounds and measured 45½ inches. The mother reported that she had had irregular menstruation every three to six months for a few days, in small amounts. Examination revealed nothing further except the continued enlargement of the breasts and nipples. There was slight enlargement of the vulva but no rosette was observed. Pelvic examination was negative. X-rays of the long bones showed some cystic changes in the diaphyses of the humeri. On Dec. 2, 1953, x-rays of the long bones showed no further changes. Dec. 12, 1953, the girl weighed 51 pounds 5 ounces and measured 47 inches. The pigmentation remained about the same. Blood pressure was 82/60. The nipples were well developed and there was considerable pigmentation of the areolae. Nov. 8, 1954, the patient weighed 59

pounds and measured 49 inches. She had no further menstruation. She complained occasionally of abdominal pain. The blood pressure was 100/70. Pigmentation was the same. On rectal examination, the uterus could just be palpated. Blood count was normal; sedimentation rate was normal. Urine was negative or normal. Feb. 17, 1955, the girl weighed 68½ pounds and measured 50 inches. She had menstruated irregularly Dec. 18, 1954, to Jan. 23, 1955, and then had a recurrence Feb. 16, 1955. She complained of indefinite recurrent leg pains. On examination the pigmentation was the same, the breasts were well developed. There was some pubic hair. Blood count was normal. Urine was negative or normal.

Fig. 11.—X-ray of right humerus, showing early cystic changes in the metaphysis.

In February, 1956, there was a marked increase in menstrual flow, with many clots. Microscopic examination of these clots showed endometrial casts with decidual reaction. On Feb. 21, 1956, the child was admitted to Columbia Hospital for further study. The blood count was normal; clotting mechanism was normal. The urine was normal. The basal metabolic rate was plus 20. Calcium was 11.1 mg.; phosphorus, 4 mg.; alkaline phosphatase, 7.3 units (Bodansky); blood pressure, 114/60. Twenty-four-hour urine specimen showed 1.4 mcg. of 17-ketosteroids. X-rays of the wrists showed a bone age of 13 years (Greulich-Pyle). X-rays of the humeri showed irregular trabecular pattern in the middle portions. The base of the skull showed an increased bone density. Pelvic examination under anesthesia revealed a mass behind the uterus. Exploration revealed an ovarian cyst in the left ovary, measuring 5 cm. in diameter. The cyst contained multiple cysts filled with straw-colored fluid of 1.020 specific gravity. The largest cyst contained approximately 14 ml. of fluid. Endometrial scrapings were taken. These revealed proliferation and some glands showing definite secretory changes. The pathologic diagnosis was normal endocervical mucosa; secretory endometrium; normal left oviduct; follicular cyst of the left ovary and luteal cyst of the left ovary.

The child made a prompt and uneventful recovery. She continued to have irregular bleeding, and on April 3, 1956, she developed measles. On April 6 she started to menstruate.

DISCUSSION

The history on this child indicates that she fulfills the typical requirements of polyostotic fibrous dysplasia as described by the various authors quoted and as elaborated by Albright. She had the onset with breast enlargement at 1 month of age. The bloody vaginal discharge began at 5 months of age. The pigmentation was noted

at that time and there was pigmentation of the aerola around the nipples and a slight development of fine pubic hair. The estrogen determination was normal. The irregular menstruation has continued to date. Cystic ovaries were found when the child was 1 year of age and again at 7 years of age. These showed luteal and follicular cysts. The vaginal smear showed luteinization. There was precocious development of the ossification centers.

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THE USE OF PEGANONE (AC 695) IN THE TREATMENT OF EPILEPSY

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IN 1938 Merritt and Putnam[1] reported that 5,5-diphenylhydantoin sodium (Dilantin sodium) was found to be the least hypnotic and most strongly anticonvulsant of a series of compounds of similar structure tested by animal experimentation. The value of this drug in the therapy of epilepsy was reported first by these workers in 1938.[2] Diphenylhydantoin sodium has survived the passage of time and at present is one of the most effective drugs available for the control of epileptic seizures, particularly major motor seizures. The major disadvantage of this drug is that it causes, in some patients, unpleasant side reactions such as ataxia, diplopia, nystagmus, hyperplasia of the gums, hypertrichosis, skin rashes, etc. Hematologic disturbances caused by diphenylhydantoin had been considered to be exceedingly rare. Agranulocytosis had been observed in a few patients.[3-5] Recently, however, at least twelve cases of megaloblastic anaemia have been reported.[6-13]

Following the discovery of Dilantin several other hydantoins have been used for the treatment of epilepsy. Loscalzo[14] in 1945 was the first to report on the use of Mesantoin (3-methyl 5,5-phenylethyl hydantoin) in the treatment of epilepsy. This drug has proved to have favorable anticonvulsant properties and is still being used. However, it has caused hematologic fatalities.[15-18] Thiantoin sodium (sodium 5,5-phenyl thienyl hydantoin) also had proved to be an effective anticonvulsant. However, this drug was withdrawn from use after four fatal cases of hepatic necrosis were reported to have occurred during its administration.[19, 20] In 1950 we[21] reported good seizure control with the use of Nuvarone (3-methyl-5-phenylhydantoin) in the treatment of eighty-eight epileptic patients. Subsequently this drug proved to be toxic to the hemopoietic system[22, 23] and was withdrawn from use.

The purpose of this present study was to investigate the anticonvulsant effect of Peganone* and also to compare its value with that of diphenylhydantoin sodium. The chemical formula of Peganone is 3-ethyl-5-phenylhydantoin. This drug is derived from the previously studied anticonvulsant, Nuvarone, by the substitution of a 3-ethyl group for a 3-methyl group. This change was made on the basis of a theory developed by Richards,[24] according to which the substitution of an ethyl for a methyl group on the nitrogen in the hydantoin or oxazolidinedione molecule would result in a somewhat less potent but also less toxic drug.

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*Peganone is being investigated by Abbott Laboratories, North Chicago, Ill.

MATERIAL FOR STUDY

This drug was administered to 108 patients who suffered from epileptic seizures of various types.

Sixty-seven of these 108 patients had never been treated previously with any form of anticonvulsant therapy. These sixty-seven patients received only Peganone during the initial observation period. Those patients, of this group, with major motor and psychomotor seizures who were not helped by the Peganone, were subsequently treated with diphenylhydantoin sodium. During the first month these patients were given diphenylhydantoin sodium in addition to the same ineffective dosage of Peganone; during the second month the Peganone was gradually withdrawn. Thereafter, these patients received diphenylhydantoin sodium only.

Twenty-five of the 108 patients included in this study had been treated previously with maximum dosages of diphenylhydantoin sodium without benefit. Peganone was prescribed to these twenty-five patients. During the first month they were given Peganone in addition to the same previous ineffective dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn. Thereafter, they received Peganone only.

In sixteen of these 108 patients the seizures previously had been completely controlled with diphenylhydantoin sodium. However, because of unfavorable side reactions to this drug, such as hyperplasia of the gums, hypertrichosis, etc., these sixteen patients were given Peganone. During the first month these patients were given Peganone in addition to the same dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn. Thereafter, these patients received Peganone only.

Eighty-eight of these patients ranged in age from 1 to 14 years, and twenty were over 15 years of age.

DURATION OF TREATMENT AND DOSAGE

The duration of therapy ranged from four to sixteen months. Seventy-two patients have been receiving the drug continuously for at least nine months.

The dosage administered varied from 750 mg. daily to 5,000 mg. daily (Table I). In each patient treatment was begun with the initial starting dosage (Table I) and the dosage was increased at the rate of 250 mg. a day every two weeks, if necessary, to the maximum dosage employed in this study (Table I). The drug was given in three to four dosages over the course of the day. Peganone is supplied in tablets of 250 and 500 mg. (¼ and ½ Gm).

TABLE I. DOSAGE OF PEGANONE*

AGE (YR.)	INITIAL DOSAGE	MAXIMUM DOSAGE
Under 6	250 mg. 3 times daily	750 mg. 4 times daily
6-14	500 mg. 3 times daily	1,000 mg. 4 times daily
Over 14	500 mg. 4 times daily	1,250 mg. 4 times daily

*Drug dispensed in 250 and 500 mg. tablets.

RESULTS

Peganone was effective only in the treatment of major motor (grand mal) and psychomotor epilepsy (Tables II, IV, V). Table II shows the results obtained in the sixty-seven patients who had never been treated previously with any form of anticonvulsant ther-

TABLE II. RESULTS OF PEGANONE THERAPY IN SIXTY-SEVEN PATIENTS WHO HAD NOT BEEN TREATED PREVIOUSLY WITH ANY FORM OF ANTICONVULSANT THERAPY*

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED NO. OF PATIENTS	ATTACKS MARKEDLY IMPROVED NO. OF PATIENTS	ATTACKS IMPROVED NO. OF PATIENTS	FAILURE OF THERAPY NO. OF PATIENTS
Major motor (grand mal)	27	9	1	1	16
Petit mal	7	0	0	0	7
Psychomotor	9	2	1	1	5
Minor motor	8	0	0	0	8
Mixed† (major motor and minor motor)	6	0	2	1	3
Mixed† (major motor and petit mal)	4	0	1	1	2
Mixed† (major motor and psychomotor)	6	0	2	2	2
Total	67	11	7	6	43

*Patients receiving only Peganone throughout observation period.
†Only major seizures affected favorably.

TABLE III. RESULTS OF DIPHENYLHYDANTOIN SODIUM (DILANTIN SODIUM) THERAPY IN TWENTY-ONE PATIENTS WHOSE SEIZURES WERE COMPLETELY REFRACTORY TO THE MAXIMUM DOSAGES OF PEGANONE ADMINISTERED IN THE STUDY*

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED NO. OF PATIENTS	ATTACKS MARKEDLY IMPROVED NO. OF PATIENTS	ATTACKS IMPROVED NO. OF PATIENTS	FAILURE OF THERAPY NO. OF PATIENTS
Major motor (grand mal)	16	9	2	1	4
Psychomotor	5	2	1	0	2
Total	21	11	3	1	6

*During the first month patients were given diphenylhydantoin sodium in addition to the same dosage of Peganone; during the second month the Peganone was gradually withdrawn; thereafter only diphenyldantoin sodium was given.

TABLE IV. RESULTS OF PEGANONE THERAPY IN TWENTY-FIVE PATIENTS WHOSE SEIZURES WERE COMPLETELY REFRACTORY TO MAXIMUM DOSAGES OF DIPHENYLHYDANTOIN SODIUM (DILANTIN SODIUM)*

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED NO. OF PATIENTS	ATTACKS MARKEDLY IMPROVED NO. OF PATIENTS	ATTACKS IMPROVED NO. OF PATIENTS	FAILURE OF THERAPY NO. OF PATIENTS
Major motor (grand mal)	18	1	0	0	17
Psychomotor	7	0	0	0	7
Total	25	1	0	0	24

*During the first month patients were given Peganone in addition to the same dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn; thereafter only Peganone was given

TABLE V. RESULTS OF PEGANONE THERAPY IN SIXTEEN PATIENTS WHOSE SEIZURES HAD BEEN PREVIOUSLY CONTROLLED WITH DIPHENYLHYDANTOIN SODIUM (DILANTIN SODIUM)*

TYPE OF SEIZURE	NO. OF PATIENTS	ATTACKS CONTROLLED NO. OF PATIENTS	ATTACKS MARKEDLY IMPROVED NO. OF PATIENTS	ATTACKS IMPROVED NO. OF PATIENTS	FAILURE OF THERAPY NO. OF PATIENTS
Major motor (grand mal)	12	2	1	1	8
Psychomotor	4	0	1	0	3
Total	16	2	2	1	11

*During the first month patients were given Peganone in addition to the same dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn; thereafter only Peganone was given.

apy: the attacks were completely controlled in nine of the twenty-seven patients with major seizures and in two of the nine patients with psychomotor attacks. All of these sixty-seven patients received only Peganone throughout the entire observation period.

As is shown in Table II, Peganone failed to give improvement in sixteen of the twenty-seven patients with major attacks and in five of the nine patients with psychomotor spells. These twenty-one patients were subsequently treated with diphenylhydantoin sodium. During the first month these twenty-one patients were given diphenylhydantoin sodium in addition to the same ineffective dosage of Peganone; during the second month the Peganone was gradually withdrawn. Thereafter, these twenty-one patients received diphenylhydantoin sodium only. As is shown in Table III, diphenylhydantoin sodium completely controlled the major attacks in nine patients and the psychomotor seizures in two.

As is shown in Table IV, Peganone controlled only one of the twenty-five patients whose seizures previously had been completely refractory to maximum dosages of diphenylhydantoin sodium. During the first month these twenty-five patients were given Peganone in addition to the previous ineffective dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn. Thereafter, these twenty-five patients received Peganone only.

As is shown in Table V, Peganone completely controlled only two of the sixteen patients whose seizures previously had been completely controlled with diphenylhydantoin sodium. During the first month these sixteen patients were given Peganone in addition to the same dosage of diphenylhydantoin sodium; during the second month the diphenylhydantoin sodium was gradually withdrawn. Thereafter, these 16 patients received only Peganone.

None of the patients who had other types of seizures (minor motor or petit mal) were benefited significantly by the administration of Peganone.

UNTOWARD REACTIONS

Routine blood counts and urine analyses were made monthly on each of the 108 patients included in this report during the entire period which they received Peganone. No abnormalities were encountered in any case.

Ataxia, diplopia and hyperplasia of the gums, seen so commonly in association with diphenylhydantoin sodium therapy, were not observed in any of these patients.

A generalized morbilliform skin rash was the only significant side reaction observed. This cutaneous reaction occurred about ten days after the first dose of Peganone was taken. It disappeared within seven or eight hours after the withdrawal of the drug. The same dosage of Peganone was given again to this patient and the rash did not reappear.

CONCLUSIONS AND SUMMARY

We have found by comparative tests that while Peganone may not possess as great anticonvulsant properties as diphenylhydantoin sodium, yet the freedom from side effects together with definite effectiveness in major motor epilepsy (and, to a lesser extent, psychomotor) should make Peganone quite a worth-while anticonvulsant. How-

ever, further study in a larger group of patients over a more extended period of time will be necessary to substantiate the value and safety of this new drug.

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MIXED TUMOR OF THE SUBMAXILLARY GLAND, TREATED BY SURGERY AND RADIATION, FOLLOWED EIGHTEEN YEARS LATER BY CARCINOMA OF THE THYROID

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MIXED tumors of the salivary glands have been an enigma for many years. Ewing used the phrase "active controversy" concerning them; hence, many pathologists do not commit themselves as to whether the tumor is malignant, beyond the diagnosis of mixed tumor of salivary gland origin.

After a critical review of the literature I do not intend, nor am I qualified, to settle this controversy; but I am referring the reader to excellent articles written on this subject.[2, 4-10] However, a case interesting and unusual from many standpoints is here reported. The patient was 12 years of age, with a mixed tumor of the right submaxillary gland. She received postoperative radiotherapy and implantation of radium tubes to the right submaxillary region, followed eighteen years later by carcinoma of the right lobe of the thyroid.

CASE REPORT

On Aug. 22, 1932, a 14-year-old white female was referred to the Brooklyn Cancer Institute (now the John E. Jennings Hospital) for radiotherapy following the removal of a tumor of the right submaxillary region. In 1930 at the age of 12 she had first noticed a lump the size of a walnut in the right submaxillary region. Because the lump did not cause her any pain, the parents did not seek medical advice until 1932, when the tumor was excised. The pathological report was "mixed tumor of the salivary gland." She was then transferred to our institution. The diagnosis was confirmed by our pathologist and the patient received 860 r units of radiation to the affected area, and again 215 r units on May 2, 1933, when a recurrence in the scar was suspected.

On Jan. 20, 1937, five years after the first admission, a tumor the size of a walnut was discovered at the site of the former operation. The tumor was excised and two tubes of 25 mc. of radon in a rubber jacket were placed in the tumor bed. She received a total of 1,800 mc. hours of radon. The pathologist's report of the recurrent tumor was "mixed tumor of the submaxillary region." The postoperative course was stormy, with a temperature up to 102° F. The right side of the face was markedly swollen, associated with trismus. The wound was reopened and drained of a purulent material. She remained in the hospital till May 4, 1937, when the swelling of her face and trismus had completely disappeared and the temperature was normal. She was re-examined in the outpatient department at three-month intervals.

On Aug. 4, 1947, at the age of 29, fifteen years after her first admission, she developed multiple, discrete nodules in the right submaxillary region and along the anterior cervical chain. This time she had a radical neck dis-

Address: 75 Prospect Park Southwest.

Fig. 1.

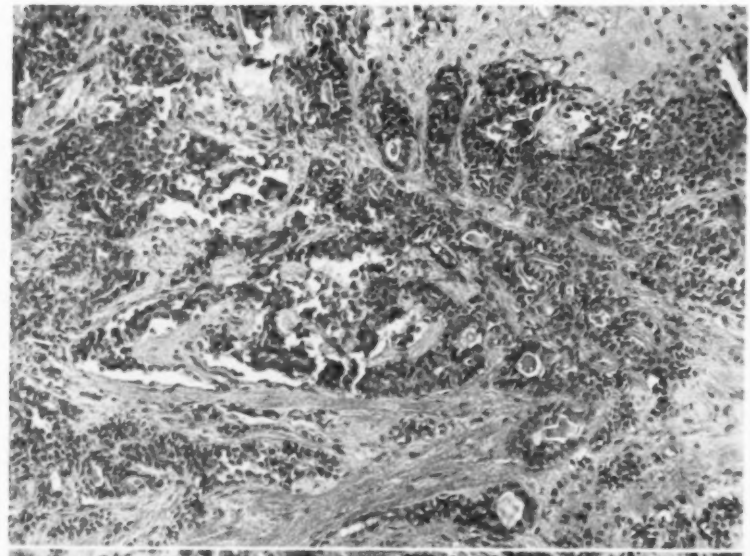

Fig. 2.

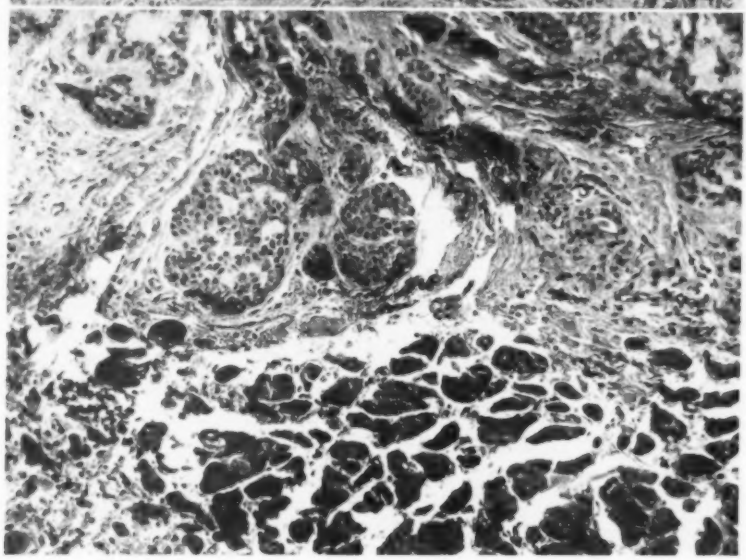

Fig. 1.—Photomicrograph showing glands and mucoid stroma in mixed tumor of submaxillary gland. (×85; reduced 1/5.)

Fig. 2.—Photomicrograph showing invasion of mixed tumor of the submaxillary gland into muscle. (×175; reduced 1/5.)

Fig. 3.

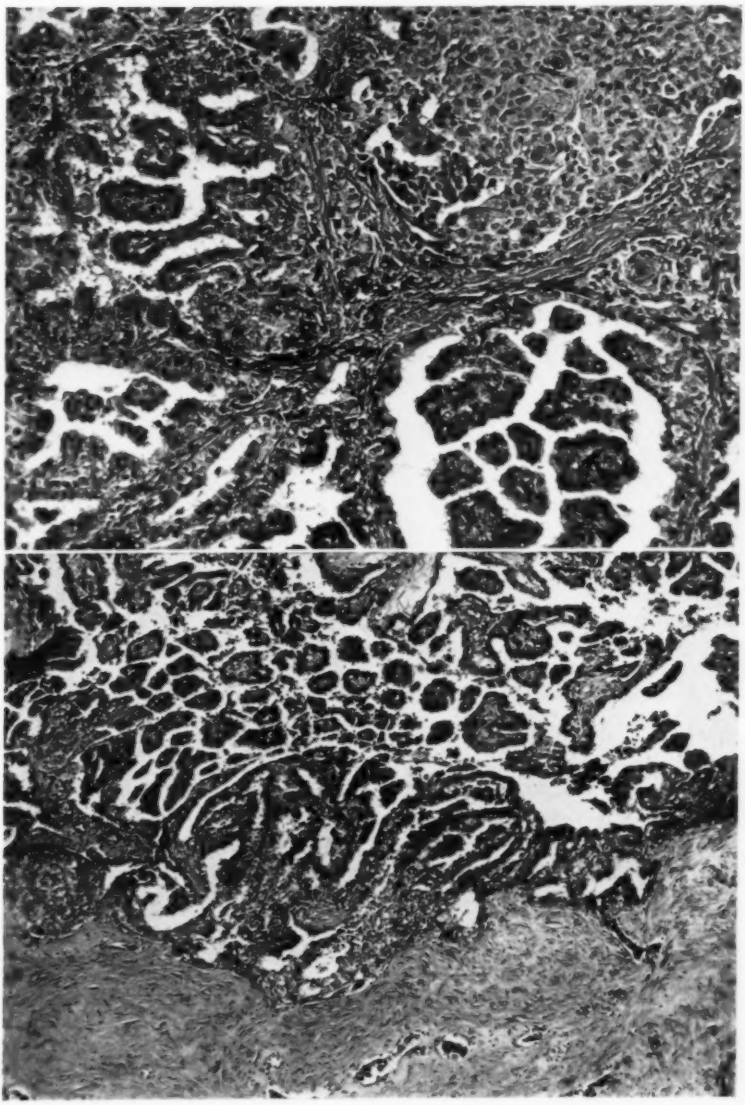

Fig. 4.

Fig. 3.—Photomicrograph of papillary carcinoma of the thyroid. (×170; reduced ⅕.)
Fig. 4.—Photomicrograph showing involvement of capsule by papillary carcinoma of the thyroid. (×85; reduced ⅕.)

section. The pathological report of all the tumors removed was "mixed tumor of salivary gland origin." The patient made an uneventful recovery and was followed in the outpatient department for the next three years.

On July 24, 1950, at the age of 32, eighteen years after her first admission, she was readmitted to the hospital for "adenoma of the right side of the thyroid." However, after thyroidectomy, it proved to be a papillary carcinoma of the thyroid. She was given postoperative radiation and again followed in the clinic. She also received radioactive iodine. The patient was last seen on Aug. 8, 1956, at the age of 38, twenty-four years after her first admission.

During the past twenty-four years she has had numerous x-ray examinations of the skeleton and lungs, including cholecystography. They were all negative for pathology. Numerous blood counts, blood chemistries, and other laboratory work were within normal limits. Her neck is free from any recurrences or metastasis. She has been married for the past sixteen years. Her menses have been normal, but she is sterile. She has an adopted son of 11, but is anxious to have children of her own. During the last examination, on Aug. 8, 1956, it was disclosed that she has a fibroid uterus about the size of a fetal head.

DISCUSSION

Mixed tumors of the salivary gland in children are rarely seen; particularly is this true for tumors of the submaxillary glands. Of additional interest is the fact that this child received radiotherapy to the right side of the neck and developed carcinoma of the right lobe of the thyroid eighteen years later. Did the radiotherapy result in carcinoma of the thyroid? The subject is of current interest.

In 1950, Duffy and Fitzgerald[3] reported twenty-eight cases of carcinoma of the thyroid in children and adolescents. Ten of the patients had received previous radiation for enlarged thymus gland some time between the fourth and sixth month of life. The authors hesitate to suggest a cause-and-effect relationship. However, they state that "the potential carcinogenic effects of irradiation are becoming increasingly apparent."

As recently as 1955, Clark,[4] reported fifteen cases of carcinoma of the thyroid in children and adolescents. All had been subjected to previous irradiation to chest and neck. He believes that association may exist between the irradiation given in early childhood and the subsequent development of carcinoma of the thyroid.

On the other hand, Warren and associates[11] reported twenty-three cases of carcinoma of the thyroid in childhood and adolescence in 1953. Only one of the patients had received irradiation of the thymus before the development of the thyroid carcinoma. The authors believe it is unlikely that prophylactic irradiation of the thymus in this case was a factor in the etiology of thyroid carcinoma.

The cause-and-effect relationship of radiotherapy as a carcinogenic factor in thyroid carcinoma in children has to be kept in abeyance until more clinical evidence is available. Meanwhile one should hesitate to prescribe radiotherapy for children in nonmalignant conditions of the head, neck, and chest as long as there are other modalities available. The case reported here is the only one on record showing mixed tumor of the submaxillary gland in childhood with carcinoma of the thyroid developing eighteen years following radiotherapy. It is hoped that it may contribute toward further study

of radiotherapy in childhood and subsequent development of carcinoma of the thyroid.

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Exercise for Infants

Neither should they be hoisted up high in the air between the hands, as some people heedlessly do; for they begin very early to be susceptible of fear; much sooner than persons not accustomed to them would imagine. It is true, they may be brought to bear pretty hearty shaking, swinging, and even jolting, by degrees; and all this is of service, when they have strength to undergo it; nay, when the child bears it well, we reckon it a good sign that it is thriving, and has been well nursed; but it should be done very gradually, and not attempted too soon. I have seen an infant almost thrown into fits, from a sudden swing given to it by one not used to young children. And how often do we see them start violently, and fall a crying, if there happens to be any sharp sudden noise made near them, in consequence of the weakness and sensibility of their nerves.

But the most useful exercise for very young infants, is rubbing with the hand; which cannot be too often repeated, nor continued too long at a time . . . There is nothing that infants in general seem more delighted with than this exercise, and it were to be wished that, the nurses would indulge them more in it. It will frequently make them quiet when nothing else will, and it is not only very pleasing to them, but conduces greatly to make them thrive . . .

From An Account of the Diseases Most Incident to Children, George Armstrong, 1783 ed., p. 174.

ATOPIC DERMATITIS IN A SCHIZOPHRENIC CHILD

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PEDIATRICIANS and dermatologists dealing with atopic dermatitis in infants are at times confronted with an unusually long duration of this condition, which may persist for many years instead of disappearing at the age of 18 months or so. In case of such a prolonged condition the psychiatrist may be called upon to treat the child. In fact, in the past few years eczema has been a concern of the child psychiatrist.

The following case illustrates some psychologic aspects of prolonged atopic dermatitis in a schizophrenic child.

CASE REPORT

Jose, a 6-year-old Puerto Rican boy whose eczema failed to respond to the usual therapy, was seen by me on the pediatric ward of Bellevue Hospital in August, 1954. Whenever he had to take a bath he had temper tantrums, refused the application of ointments, scratched himself constantly, and was extremely restless.

Upon his return home from his first stay in Bellevue Hospital (his ninth hospitalization) he had to sleep with three of his siblings (two brothers and a sister). The attitude of his family toward him was one of rejection and annoyance, an attitude of which he was aware. On one occasion they even refused to take Jose back home after one of his many hospitalizations. He referred to his parents as "he" and "she." When seen (1954) he already was preoccupied with auditory hallucinations, was afraid of noises, and made reference to someone knocking on the window.

Physical Examination.—The neurological examination was essentially negative. The dermatological condition remained practically unchanged. There were scaling and crusty weeping lesions in the popliteal areas, behind his ears, on the upper lip, around the eyes, and on the scrotum. A moderate adenopathy was present and, in addition, a mucopurulent nasal discharge. The x-rays showed paranasal sinuses underdeveloped. No allergens were found to precipitate the disease.

At different times during the previous six years he had received penicillin, Aureomycin, bacitracin, Tarbonis, ACTH, cortisone, Benadryl and many other antihistaminics. The administration of these drugs resulted in questionable and short-lived improvement.

He whirled gracefully and liked antigravity play. He was extremely clinging to adults and was so small that it was easy to mistake him for a 3-year-old child.

At first his condition seemed to improve when he was hospitalized; however, his previous eight hospitalizations had been of short duration and when he stayed on the psychiatric ward for several months it became apparent that his skin condition was not responding specifically to the difficulties inherent in the home environment but to any environmental stress. This stress had diminished when he was babied during the first few weeks on the ward, but he would become more and more demanding and when his demands could not be met the dermatitis worsened.

From The Psychiatric Division of Bellevue Hospital, and The Department of Psychiatry, New York University College of Medicine.

Family History.—Jose was the fifth of seven children. He was born in Puerto Rico while his father was in the United States. According to his mother, his development was "normal" except that at 4 months of age he developed a generalized eczema which resulted in a series of hospitalizations. No other member of the family on either side has been known to show any skin sensitivity or any allergic condition.

The family stayed in Puerto Rico till Jose was 2 years old, during which time he never saw his father. The father was 32 years old when Jose was born, and was a dominant figure in the family, although an irresponsible one. He resented the fact that he could not work as merchant seaman, giving as a reason the inability of his wife to do the shopping without him. He abandoned his job as a night taxi driver because it made him nervous. Finally he went again to sea, without making provisions for his family and knowing that an eviction notice was pending.

The mother seemed unaware of the world around her and had little to say to her son on rare visits to him in the hospital. Her favorite child was the baby daughter.

Clinical Findings.—On the ward the boy was most untidy. Most of the time he lay on the floor, scratching his lesions. He was dirty, even a few minutes after a bath; his clothes were always messy. Jose believed that he had the "scratch" because of his lying on the floor. At times he wanted to keep the "scratch," believing that it might help him to stay in the hospital. At home Jose demanded all of his mother's attention and clung to her continuously. On the ward, however, he never mentioned his parents. When asked where he would prefer to stay he would give a different answer each time, vacillating between wishes to go home and to stay in the hospital.

During the first psychiatric interview he was in constant motion, climbing beds, windows, and chairs, kicking and attacking the psychiatrist. He finally became interested in drawing but refused to answer questions. The only time he became quite confident was at antigravity play. This he enjoyed very much and demanded constantly. Jose told the psychiatrist that he had seen Captain Video on the roof of the hospital and that the Captain said "Hello." Not for a moment did he doubt the accuracy of his perceptions. In addition, Jose showed confusion of identity. When sitting on the nurse's lap he said that his right arm and right leg belonged to the nurse (his right shoulder was directed toward her) and his left arm, to a boy.

He wanted to be a girl and liked nurses better than doctors. On other occasions he refused to play with girl dolls and asked for boy dolls. He would put the boy doll on the girl doll and make them "kiss."

He assured the psychiatrist that inside his head were macaroni and cheese. At times, after drawing a devil he said it was macaroni. In his chest was God and God told him to be a good boy. Jose believed "that his best part were his shoes because he could run in them." His worst part was a piece of iron with which he would hit the walls of the office, especially if there were any concavities or convexities.

Telling about his dreams, Jose mentioned alligators that ate him up. At times he wished that his "scratch" would not come back; on other occasions he did not want to be free of it.

His fantasy life was extremely vivid and very real to him. He told about his brother throwing a knife through the window, and killing his mother's girl friend. The brother accused Jose of killing her and said that policemen were looking for both of them. However, a policeman said that he would not arrest Jose because Jose might "give" him the "scratch."

Jose could hear a man and a boy devil talk about wanting to kill him. "In front of my window they ate my

father, my mother, and my sister but they didn't catch me." (His window was on the sixth floor.) The boy took everything personally, talked about the "bad things" the boys on the ward did and blamed on him. This paranoid attitude caused his isolation from the rest of the children on the ward.

Psychologic Examination.—Jose's attention span was short, and he had to be bribed to do verbal and abstract tasks. On the test the boy did not seem to make a positive identification. On the Rorschach he saw the parental figures as fearful, always angry and potentially harmful (gorillas that can kill and mad witches); moreover their behavior was unpredictable. Jose was hostile and aggressive toward the rejecting world and, being unable to accept his aggression, as well as being afraid of his destructive impulses, he projected these feelings to the people about him. His fears were revealed in the answers he gave. For example, to the question "Why are houses needed?" Jose answered, "Because if not, murderers will come in and kill you." Fantasy became so real to him that he was not capable of discriminating between it and reality.

Despite his average intelligence (I.Q. of 97 on the Wechsler Intelligence Scale for Children being considered minimal because of the short attention span), his Bender-Gestalt figures were poorly organized and showed extreme impulsiveness. Performance on the Goodenough figure-drawing test was at the level of the mental age of 6 years (his chronological age), but it was deviant and bizarre and revealed a very confused body image and distorted self-concept.

Course in the Hospital.—It was noticed after a few months on the ward that when he was in a better mood Jose's eczema would be less pronounced and his scratching diminished. We tried to discover what he liked best and without doubt it was to cling in a regressed, infantile way to the nurse while being fed. Because of this obvious craving for affection and the lack of it in his own family we decided to follow his cues and thus allowed him to regress under supervision. He was given milk from a bottle. This took place in a room where no one was allowed except the nurse. The patient knew how to limit this regressive experience and seemed to be aware of the "make-believe" quality of the situation. He insisted on keeping it a secret. After a few weeks he removed the nipple but still drank the milk from the bottle.

In the use of "guided regression," according to Augusta Alpert,[1] one naturally may be concerned with the danger of infantilizing the child and with contagion in the group. In the present case neither danger materialized. The child limited his regressive occupation himself. He would drink from the bottle like a baby, then "grow up" suddenly and rush off to more attractive tasks, such as pretending to read nursery books.

Although no psychotherapy in the formal sense was attempted, we considered play and talk as a form of therapy. Often it may seem to the observer that much time is wasted this way, but Edith Buxbaum[2] points out that the relationship to a friendly adult has a stabilizing effect upon the child who lives in a hospital with less fear, anxiety, and uncertainty than in his own home. If he needs to test limits, he can do so without fear of retaliation or actual danger, and gradually he can reach a stage which permits him to learn something new. The above observations applied well to Jose and as time progressed we observed that his behavior improved and, although his eczema never cleared entirely, it was less extensive and he scratched less. After a short visit home the parents placed him in a psychiatric treatment center, admitting finally (after seven years) that they really did not want this child in the home.

DISCUSSION

It is impossible to say whether the first attack of atopic dermatitis, at the

age of 4 months, was a biological accident or whether it was related, in some subtle way, to the patient's reactions to early deprivation.

Also it is questionable whether the mother gave the newborn Jose the same care as that given to his siblings, in view of the father's desertion which coincided with his birth. The patient's first eruption was probably a simple infantile eczema; on the other hand, we know that even infantile eczema may have an important emotional component.[3] In any case, the recurrence of the eruption and its perpetuation seem definitely to be related to the persistence of scratching activity.

Some psychiatrists would interpret the significance of the disfigurement of the patient's skin as representing a barrier to almost all human relationships. It is perhaps justifiable to assume that he had a need to make himself as unattractive as possible because of his extreme guilt feelings and so, systematically, ruined his face through scratching.

It is also possible that the patient was striving to be loved despite his "scratch." On the other hand, he had great contempt for his peers, whom he disliked and against whom he developed paranoid ideas, wanting to give his "scratch" as punishment for his rejection.

LITERATURE

The literature on the subject of eczema is extensive. According to some students, infants with eczema are infrequently held and it is thought that this factor may have a causative effect on infantile eczema, suggesting that the central nervous system may play a significant role in the pathogenesis of this entity.

Sherman and Sherman[4] maintain that the face is the most sensitive area of the infant's skin. If this is true it may explain why in infants the face is more often involved than the legs. However, in the case reported, the legs and the popliteal area, as well as the face were involved.

Many psychiatrists believe that most infants with eczema have received an inadequate amount of soothing physical contact with their mothers. Because of this fact, we must assume that a much higher proportion than usual of the skin experiences of these infants have been inadequate. Thus, these infants would have a greater reason for attempting to insulate their skins from the external world. The insulation, of course, would tend to prevent all sensation, good and bad alike. English[5] says that it is not true that all infants who have had inadequate caressing and fondling develop eczema; therefore, other factors, either constitutional or allergic, may be involved in every case. The eczema might not have occurred had the mothers of the eczematous children given their infants more cuddling.

On the other hand, not every poor mother-child relationship leads to infantile eczema. Bakwin,[6] describing infants with "hospitalism," does not mention eczema as a manifestation. As is well known, children with "hospitalism" have not been fondled enough, and thus it is hard to ascertain that lack of soothing skin contacts is the sole significant factor in those who get eczema.

The skin may, in many cases, be selected as a somatic area for emotional conflicts. English[5] speaks of a "longing expressed in the skin by itching

which calls for the soothing hand." The hand which scratches is the soothing hand, temporarily at least.

Jelliffe[7] regarded eczema as a longing of the skin for caressing.

Although dermatologists frequently see no evidence that psychological factors play an etiological role in eczema, the psychiatrists for the most part feel that the psychic factors may exert a causative influence. Most observers agree that psychic factors can aggravate the disease.

Rogerson[8] found that a majority of children with eczema showed excessive motor activity, an unusual amount of anxiety, and pronounced irritability and aggressiveness.

In view of a severe emotional disturbance, present in many cases of atopic dermatitis, a differentiation of this condition from schizophrenia seemed indicated. Schur[9] attempted to do it in his paper, "Comments on the Metapsychology of Somatization." The case under discussion, however, is an illustration of how both eczema and schizophrenia can coexist.

The dynamic formulation of the psychosomatic aspect of atopic dermatitis was given by Deutsch and Murphy.[10] They say: "In considering constitutional elements there is evidence that true atopy has a genetic basis and is due to a nonspecific dominant gene in combination with a specific codifying gene which may be brought in by a normal parent who lacks the main dominant gene." They suggest that the tendency to react in a specific fashion may be latent and produce no symptoms, since the different components of the fusion between the two genes may not always be activated.

Depending upon the strength of the biological hereditary factors and the duration of the childhood disease process, as well as the amount of gratification obtained, the psychic development may become distorted or arrested. If scratching or touching is prohibited (our patient's hands were frequently tied before he came to Bellevue Hospital), tension tends to develop and the course of the illness may be prolonged or pathologically stabilized.

The effect of the disease process on the parents should also be considered, as well as the repressions of their attitude toward their skin and that of their child. It is not easy for parents to cope with a chronic case of atopic dermatitis in their child. There is little wonder that tension mounts with every exacerbation of the skin lesion and, as the skin lesion becomes worse after scratching, a vicious circle is established.

It requires an unusual amount of self-sacrifice on the part of the parents and siblings to be able to maintain a good relationship with such a child who, after all, is different in his appearance and personality.

CONCLUSIONS

Following his ninth hospitalization for atopic dermatitis this 6-year-old boy was placed in a psychiatric treatment center where his skin condition improved greatly. After one year (1955-1956), there remained only minimal lesions around his ears and only once did he come to the attention of the pediatrician because of his dermatitis. Jose is getting psychotherapy on a once-a-week basis and seems to respond to it favorably. He takes part at present in the regular school curriculum and is not a management problem.

His father visits him twice a month and still refuses to have him home,

claiming that it would result in additional hardship for everyone concerned.

In the above presentation an attempt was made to draw attention to the psychologic implications of atopic dermatitis. I have tried to point out that in addition to the genetic etiology, a psychogenic etiology of this condition is also an important factor.

A possibly favorable response to psychotherapy should be considered in the cases of eczema resistant to the usual treatment.

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A Receipt to Cure the Itch

Take four ounces of crude brimstone, two drachms of sal ammoniac, finely powdered, and with a sufficient quantity of hog's lard work it up into an ointment. This ointment, rubbed well on the parts affected, will be attended with the desired success, though the disorder be never so inveterate; and for ease, safety, and expedition, gives place to no application whatever that can be made use of to remove that troublesome complaint.

HUTCHIN'S IMPROVED: BEING AN ALMANACK, 1774.

CAVERNOUS HEMANGIOMA OF THE SCROTAL SEPTUM

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CAVERNOUS hemangioma of the scrotum is a rare tumor, with only twenty-five cases having previously been reported in medical literature. I would like to add one more case, which is unique in that it is only the second reported case of the hemangioma being limited to the scrotal septum and concerns the youngest patient in which such a lesion has been found.

CASE REPORT

The patient, aged 2 months, was referred for treatment by his family physician, who had found an intrascrotal mass at the age of 1 month. The mass was gradually increasing in size. Examination of the patient revealed a hard, irregular mass, about 1½ cm. in diameter, located within the scrotum, between the testes but entirely separate from both testes. A small pedicle was palpable, attached to the mass and extending up through the posterior portion of the scrotum, in the midline, into the perineum. At operation, a 3 cm. long elliptical incision was made in the most ventral midportion of the scrotum, overlying the mass, in order to remove with the tumor any scrotal wall adherent to the tumor mass. The mass was freed with ease of surrounding fascia and was found to involve the scrotal septum. The uppermost portion of the mass was attached to a vascular pedicle consisting of two small veins. The pedicle was ligated and transected and the mass removed with overlying scrotal skin. The wound was then closed. The pathological report of Dr. S. J. Rose of St. Michael's Hospital, Newark, N. J., identified the growth as a cavernous hemangioma.

DISCUSSION

Cavernous hemangioma of the scrotum was first reported by Robert[1] in 1851. In 1937, Gibson[2] reviewed the literature and found only eighteen reported cases and added another. Since then, cases have been reported by Mintz,[3] Bouteau and Dubarry,[4] an example of angioma of the intertesticular septum, Schulte,[5] de Freitas,[6] Baurys and Morton,[7] and Mason and associates.[8] This makes a total of twenty-five previously reported cases of hemangioma of the scrotum and with only one of these cases was the hemangioma within the scrotal septum.

Gibson divides hemangioma of the scrotum into two groups: (1) hemangiomas of the skin; (2) hemangiomas of the subcutaneous tissues.

The characteristic feature of hemangiomas of the first group is multiple, protruding, violaceous skin nevi containing engorged vessels and having hyperkeratotic surfaces resembling a verrucous condition.

Group 2 hemangiomas, since they may not show any skin changes, and vary in consistency, are difficult to diagnose. The mass may be limited to one portion of the scrotum or may be extensive, with possible involvement of the perineal tissues.

Cavernous hemangioma is usually seen in the first or second decade of life, but may appear at any age. Our patient is the youngest reported, with

the mass first being noticed at 1 month of age. The etiology is unknown, but seems to be on a congenital basis, with trauma as a possible exciting factor. Hemorrhage has been reported. The hemangioma gradually increases in size if not removed. The only effective treatment is complete excision of the mass.

In the patient of King[9] the growth emptied into a single vein. Winslow[10] and Johnson[11] found two large veins extending from the hemangioma into the perineum in the angle between the bulb of the corpus spongiosum and the rectum. Holmes[12] and Hewitt[13] treated their patients by ligating a pedicle attached to the hemangioma, and Gardia[14] traced the veins in his patient to their junction with the internal pudendal veins. I also found the hemangioma to be attached to a pedicle of two veins that extended into the perineum. Care must be taken in resecting the tumor to ligate the vascular pedicle.

SUMMARY

This is a case report of a cavernous hemangioma of the septum of the scrotum in a 1-month-old infant. Cavernous hemangioma of the scrotum is a rare tumor, with only twenty-five cases having previously been reported. This case is the youngest reported, and only the second reported case of hemangioma of the serotal septum.

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Special Article

PSYCHOLOGICAL IMPACT OF LONG ILLNESS AND DEATH OF A CHILD ON THE FAMILY CIRCLE

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IN THE practice of comprehensive medicine, the care of the total patient is stressed. In pediatrics, this concept must be expanded to include the total family circle. Such an approach to practical medical problems and practices in the treatment of children with lymphoma and leukemia would include the recognition and consideration of the psychological impact of the disease and the death of the patient on the family.

Members of the pediatric staff at the University of Texas M. D. Anderson Hospital are alert to these psychological implications, and attempt to cope with them with the same thoroughness accorded problems of physical comfort of the patient. The interest of the staff does not stop with the last final sentences in the medical record: "The patient expired quietly. Autopsy was performed." What of the lasting impact of this long period of "living with death" upon the family? What is the process of rehabilitation of family living patterns disrupted by long separation and death? These questions have been asked of a small population of parents of children who have died of cancer after prolonged illness. Their responses have been analyzed for the purpose of setting up a systematic long-range investigation of the psychological impact of illness and death on the family.

The answers are of interest now, however, because they seem to indicate important trends in the thinking and philosophy of the families represented. We are interested in four major categories:

1. Reactions in retrospect to the long terminal stage of illness characterized by intermittent remissions and regressions, and eventual death of the child.
2. Impact of enforced separation and disruption of family living on the marriage and the siblings of the ill child.
3. The psychological impact of death on other children in the family.
4. The role of religion in the tolerance and acceptance of the illness and death of the child.

For the sake of brevity, the responses will be reported as trends of the total, and then illustrated by excerpts from statements of the parents.

REACTION TO REMISSIONS AND REGRESSIONS FOLLOWING EXPERIMENTAL TREATMENT

Pediatricians who watch the brave battle waged by a dying child re-

From the University of Texas M. D. Anderson Hospital and Tumor Institute.

sponding to treatment for a few days and lapsing into regression and suffering, only to be pulled out of the relapse once more with the administration of a new drug, but with the certainty of impending death ever present, sometimes wonder if they are right to continue to pull the child back from what might be a merciful death. What do the parents feel about this grim battle six months afterward?

The consensus of the twenty parents responding seems to indicate that looking back, they were most grateful for the few months, weeks, days, or even moments with their child, so long as there was hope, and so long as the child's suffering could be controlled. One mother said, "Each day, even each minute is precious." The universal feeling seemed to be, "maybe my child will be the one to get well." There was common agreement, however, that when the time came that only suffering could be predicted, it was the wish of the parents to prolong the life no longer.

Specifically, the mother of a 6-year-old girl who was in the hospital for fourteen weary months, said:

Sometimes it seemed worse on the child to get better and then start all that suffering over again when all of it was so hard for them to understand. But she had as much hope as we did. She was always talking about when she'd get to run and play like other children.

Yes, I built up false hope time and again. I know it was impossible to cure her, but in my heart I felt that maybe my child would be the one to get well. I think it helped me to get more prepared for the dreadful thing that was to happen.

The father of this child said:

While there is life there is hope. . . . We were always anxious to see the results of their experiments because that was our only hope . . . something new.

Turning to another family, this time the mother and father of a 3-year-old girl, with two older sisters. The mother speaks:

The knowledge that my child received all the treatment that medical science had to offer has been a great comfort to me. There are no "ifs" in my mind that she might have recovered "if" we had only kept trying. It is true that you build up false hope during the periods of remission, but I would not have wanted to miss that last year of her life.

It seems to me that it was during that year that we really got to know Jenny and if I had to do it over again, I would want the doctors to keep trying.

If I could have spared her the last two months of her life, I would have, but I don't believe this period could have been avoided if at any period the disease had been allowed to progress. As it was, except for those last two months, there were only three or four weeks during that year when she was really ill.

The father concurs:

Yes, I built up hope, false or not, during the remission periods. This hope made it easier to bear, since it provided a renewal of strength each time. Hope made a reason for continued effort.

Another mother of a 6-year-old Mary said:

Our child had only one period of remission, and we cherish those three months beyond words. We had enough hope restored that we were able to lead a normal life, but not enough that it shocked us when the disease returned. We feel that the doctors gave us three wonderful months with our child, for without treatment she almost surely would have gone sooner.

Now, had she remained alive during several of these periods, and had she done a lot of suffering . . . I don't know. I do know that we have said many times, "Thank God, He took her on and she didn't have to suffer." Looking back, another six months of life would have meant very little, if it had held a lot of suffering for the child, and that

kind of memories are awfully hard to live with . . . and next to impossible to sleep with.

Thirteen-year-old Sarah's mother expressed a common sentiment even when the child did not respond to treatment.

She was never better after the mustard gas was given her. She was never as well again. Should it have been given? I don't think so in her case, but I can't say for sure. Had it only been one chance in a million, I would have taken it.

A father summarized a common hope for an eventual cure, and his reaction to the frustration of false hope:

It was terribly disappointing and discouraging to find these hopes were false, yet it helped us to press on, *hoping that a cure could be found and our child made well.*

IMPACT OF ENFORCED SEPARATION AND DISRUPTION OF FAMILY LIVING ON MARRIAGE

The consensus seems to be that if the marriage is a good one, this stress of long separation and illness serves to draw the two partners closer together in this fight against a common enemy. This is not always true. Four couples of the twenty contacted were known to have conflicts. Two couples, known to be having stormy weather, did not respond to the inquiry. In the case of another, observed to be growing farther apart on the wards prior to the death of the child, only the father responded. He acknowledged no strain on their relationship. In the fourth marriage in question, both partners responded.

The wife said:

It seemed to me that we were bound closer together with a stronger love for each other as well as our family. We were brought to realize something we had always taken for granted.

The husband, however, pointed up a sore spot that had not healed:

There was one problem that it seems all fathers and children are faced with, and that is the possessive spirit that the mother or wife seems to be obsessed with, in that she will not leave the sick bed except on rare occasions, even if the children or husband are there to watch over them.

On the positive side, a wife who stayed away from her family for fourteen long months to stay with her dying daughter, said:

We needed each other's comfort as we'd never needed it before. We very seldom thought much about ourselves and how many miles apart we were. It was just of losing our little girl and what we could do to make her happy. We needed each other's strength and love and comfort to keep going.

One interesting incident was reported which seemed to indicate that in some cases sharing this common danger to a loved one actually changed the family pattern of living to a happier one.

The wife speaks:

"You'll never know just how much closer this has brought us together. Before, my husband didn't seem to take much interest in his family, he hardly ever noticed the children. God has given us a baby girl since we lost our little boy, and he just doesn't seem like the same man. The only thing is, I hate it that it had to be something like this to wake him up.

In other cases, the ordeal did not seem to bind the marriage closer, but as one wife put it:

My husband and I have always been close and I can't say that this experience made us closer. There were problems, of course, but not *between* us. This was something that had to be faced and we each did what we had to do.

Perhaps the most beautiful description of what happens to a marriage

under this sort of stress was given by the mother of a 13-year-old girl, who died after a nine-month illness.

We had been married long enough to know that as storms occur in nature, followed by calm, so also storms occur in married life, but peace and calm come again if the union is built on a mature love that expects perfection of no person. As the tides go out, leaving us bitter and dry, wait a while, again they will return. We "twain are one flesh." What hurts one hurts both. The problems in marriage . . . or life, for that matter . . . are not created by outside circumstances, the problems rise from within the victims of the problems, rise from within themselves and burst forth as problems.

EFFECT OF SEPARATION ON CHILDREN

The honest, sincere way that each parent tried to deal with the problem of leaving their other children at the time of the illness and death of a brother or sister was truly wonderful. They were certainly in agreement as to keeping the other children happy. Despite this effort, the reports indicate that there have been ill effects on the children.

One mother reported:

It was very hard on my other children living with first one aunt and uncle or grandparents all that time. They saw their daddy every week or so, but with me it was only the Christmas we brought our little girl home and one other time that they came to Houston. It didn't bother our six-year-old boy as much as the 12-year-old boy at the time. It was easier for him to get adjusted anywhere. However . . . after we started the little boy to school, he seemed so far behind the others. The teachers said his IQ was above average, but he was just immature. They seemed to want us to take him out of school until he was more mature, but we didn't, and with our help and the teacher's, he is beginning to do better.

The father said:

I don't think it affected our oldest boy very much except being lonesome for us and having the entire family together. But the youngest boy was bothered quite a bit by the separation. In fact, it seems to me . . . or us . . . *that he just lost that much time.* I just don't know what should have been done to prevent this. He was with several families during this time and *just seemed to have stopped and waited for us.* He seems O.K. now, but just a couple of years behind his age.

REACTION TO DEATH

The psychological impact of death on the young child is a subject that we know too little about. How to prepare children for the death of a sibling is a problem parents of leukemic children must face. The following excerpts tell a brave story of how a few children and their parents met this problem.

A father said:

Our oldest boy was 14 and he bore his feelings a little better than our youngest son who was 10. This younger one lost his appetite and wandered around in a daze for several weeks.

The mother of the child who lingered for fourteen months reported:

Two of my brothers told my boys what had happened, and, of course, they were broken hearted because they had just worshipped their sister. When we got home, my oldest boy never mentioned it, but he stayed with us every minute. The youngest boy talked constantly about her and asked us questions. Some of my folks tried to stop him, but I thought it best to let him talk, even though it hurt me very much. I thought they should decide whether they wanted to see her, or remember her as she was, and about the funeral. They wanted to see her, but they didn't want to go to the funeral. I don't think parents should make children that young go through something like that. I think it's better to explain and talk to them if you can.

The father said:

I am sure the older boy did a lot of thinking but he doesn't have too much to say. He

is very careful not to even say anything about it. But the other one talks more because he really didn't know too much about everything. And he just talks a lot anyway.

The mother of a 3-year-old girl who had two older sisters said:

They were very sad, of course. They did not want to see her after she died, but I insisted and I'm glad that I did. The fact that they saw her restored to some semblance of normalcy helped, I think, to erase the picture of her when she was so ill.

We encouraged them to return as quickly as possible to their own activities and they did not seem to have any difficulty in doing so. They both have a picture of Jennifer in their room by choice and though they do not speak of her often, I know that they have not forgotten her. In glancing through my oldest daughter's (now almost 17 years old) date book the other day, I noticed that on April 14, she had written "Jenny's birthday."

They show more concern for minor illnesses in themselves than children would ordinarily. We have tried to be patient and have made numerous trips to the doctor to reassure them.

A mother said of her grown son:

I don't know what went on inside him. We never do understand another's "insides," do we? But he went on with life about the same, except he acquired a hobby of working with tropical fish . . . she loved them.

Perhaps the most helpful advice to other parents was given by 6-year-old Mary's mother.

Death was a new experience to our children, as they had never lost a relative before. Comfort them as you can, but let them do as they want. For instance, our little boy . . . who was 8 at the time . . . would kiss his hand and rub her face. Useless, yes, but it gave him comfort. During the funeral, he repeated over and over, "Oh, Mary! Mother, we will see her again, won't we?"

Reassure them; explain to them; answer their questions. People react differently to death. I found it most helpful to talk about my child. Maybe talking about it will relieve tensions of the other children. If they want to talk about it, let them. Don't urge them to visit the cemetery, if they prefer not to. Help them to think of the departed one as being alive in a place of beauty . . . not in the cemetery.

THE ROLE OF RELIGION

The consensus seemed to be that "without religion I would not have had the courage to live on." A mother, assisting in the preparation of this material, said after reading the responses:

The true Christian spirit, the humbleness and the absolute acceptance of "Thy will be done," and the desire to live a better life, made one wish that every agnostic or atheist could read these reports. Truly, one's religion is the only thing that keeps us sane at this time. Even then, it is difficult, but with God's help we can meet our problems so much better.

This was not a unanimous feeling, however, for on the negative side, one mother said:

I have been taught since childhood that there is a life after death, and I felt after Jennifer's death that she had left us, but not that she was dead. I was not tolerant of the illness, but had to accept the fact that she was gone. I am not bitter toward God, but I do not depend on religion or the church as much as I used to. I have wondered many times if there was a reason for what she had to go through and wish that it could be revealed to me, if there is one. I think that my husband and I both needed spiritual guidance during this period. Our church and its pastor did not provide it.

The husband, however, did not feel this way. He said:

Many have traveled this same road before me and many since. I have not been alone in sorrow and loss. Much consolation and encouragement came from those with similar experience. Many acts of kindness, many prayers offered on our behalf by Christian friends comforted nerves and distraught mind.

Faith in God makes me understand that things past, present, or future never have been or ever will be as we want them. To balk against this rule would lead to bitterness and despondency. I am convinced that though my prayers, my hopes, and my desires for the child were not to be, yet a new and better life has opened for her.

There seems to be a period endured by the parents when rebellion against death is paramount, but, eventually, as one mother put it,

I stood by the side of his little bed and I prayed if he couldn't get well, and if he had to suffer, I asked God to take him, for he was too small to understand, and it was God's will that he was taken.

It was as if following the desperate struggle to keep the child, once the parent was able to say in sincerity, "Thy will be done," some sort of peace and acceptance descended. One mother said it rather succinctly:

At first, I resented God because he took my baby, but now I feel that God knows best, and we think a lot about living where we will be ready to meet him when God gets ready for us.

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THE patient was a 36-hour-old white baby girl who was referred to this hospital because of jaundice that appeared within the first hour of life. She was the second child of a 25-year-old mother whose previous child was normal. Her present pregnancy was uneventful, the membranes ruptured spontaneously "more than twenty-four hours" before delivery, labor lasted thirty hours, and delivery was by breech extraction. The placenta was twice the normal size. Respirations began spontaneously. The birth weight was 5 pounds 8 ounces. On admission to the nursery the baby was breathing rapidly and shallowly but without retractions. Moderate jaundice was present, and the skin showed multiple purpuric and petechial spots. There was oozing of blood from the tongue and gums. During the first thirty-six hours the jaundice increased, and penicillin, streptomycin, Hykinone, and cortisone (two 25 mg. doses) were given, and the baby was transferred to this hospital.

On physical examination the temperature was 97.4° F., the pulse 132, and the respirations 60. The body length was 46 cm.; the head measured 32 cm. The anterior fontanel measured 2 by 2 cm. and was depressed. The chest measured 30 cm. The weight was 5 pounds 1 ounce. The baby was breathing rapidly but without retraction or flaring. The skin was deeply icterie, with widespread purpuric spots and numerous intracutaneous nodules. The sclerae were deeply jaundiced, and the fundi could not be seen. The heart was slightly beyond the left nipple line; a soft apical systolic murmur was heard. The spleen was hard, 6 cm. below the left costal margin. The liver was 3 cm. below the right costal margin. There was no opisthotonus, and the Moro reflex was active.

Urinalysis revealed a 3 plus bile, 5 to 10 white blood cells per high-power field, and a green reduction reaction; the urine was otherwise normal. Nose and throat cultures and two blood cultures showed no growth. The blood hemoglobin was 16.4 grams per cent, with 25 per cent reticulocytes. The serum bilirubin values were: at twenty-four hours, direct 17.2 mg. per cent, total 27.2 mg. per cent; at thirty-six hours, direct 12 mg. per cent, total 25 mg. per cent; at thirty-eight hours, direct 8.4 mg. per cent, total 33 mg. per cent. The

baby's blood was group O Rh-positive. The Coombs test was negative. The mother was group O Rh-positive. No Rh antibodies were present in either the baby's or the mother's serum. The Coombs test on the baby's cells after incubation with the mother's serum was negative. The mother and the baby both had negative Hinton tests. There was no erythrophagocytosis of the patient's incubated cells. There were only a few normoblasts and erythroblasts seen on the patient's smear. The father's hemoglobin was 16.0 grams per cent, 0.5 per cent reticulocytes; the mother's reticulocyte count was 1 per cent.

The patient was given aqueous penicillin, 200,000 units intramuscularly every six hours, streptomycin 50 mg. immediately and 20 mg. every six hours, Chloromycetin 75 mg. intramuscularly immediately and 40 mg. every six hours, Hykinone 1 ampule immediately and 1 ampule on the second hospital day, and cortisone 25 mg. intramuscularly every eight hours. An exchange transfusion with 500 ml. of fresh, group O Rh-negative blood was performed between 36 and 38 hours of age. The baby's activity remained fairly good, but when the bilirubin again rose at 48 hours of age, a second exchange transfusion was performed. After 200 ml. was exchanged the baby became worse, with irregular heartbeats and cyanosis. After some improvement another 80 ml. was exchanged slowly, at which time the pulse and respirations ceased.

DISCUSSION

DR. CLEMENT A. SMITH*.—I think this is one of the several cases in which we will learn more after we have the pathologic findings than before. I hope the discussion will not end with my remarks, but will really begin there.

The membranes ruptured twenty-four hours before delivery. We have learned that this does not necessarily result in infection of the infant, though we always mention it as a possibility.

The fact that this was a rather small baby for a full-term one, and that she became ill fairly soon after birth, may indicate that she was afflicted with some illness in utero. The presence in the skin of multiple purpuric and petechial spots and the oozing of blood from the tongue and gums are, of course, events that do not happen in any normal infant.

During the first thirty-six hours, while the baby's jaundice increased, a battery of therapeutic procedures was tried in an attempt to influence the supposed infection and the obvious bleeding that were present; but nothing seems to have altered the child's course.

The pulse and respirations on admission here were a little fast, but were no faster than those of many normal infants, particularly if they are not sound asleep. I would expect the fontanel of an infant at that age, who has had nothing to eat, to be a little depressed; certainly the important thing about the fontanel was that it was not bulging. I would like to know more about the purpuric spots and the intracutaneous nodules. If the nodules were areas of bleeding into the skin they would be more easily understood.

DR. ROBERT HAGGERTY.—That statement is not quite clear, and I suspect

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that the nodules were associated with the purpuric spots.

DR. SMITH.—If not, I cannot explain them. The slight enlargement of the heart, beyond the left nipple line, and the soft apical systolic murmur do not help me by pointing to any diagnosis, and I am more interested in some of the other findings, such as the hard spleen and liver. The latter was not particularly big for a newborn baby. I wish we knew more about its firmness. A firm liver would be a more striking finding than a soft liver extending only 3 cm. below the right costal margin. The baby had no opisthotonus and had an active Moro reflex, so that there was not much indication of neurological disturbance.

The urine contained 5 to 10 white cells per high-power field, which I suppose was from a centrifuged specimen. In the urine of a baby girl so few cells are not usually important. The green reduction reaction obtained from the urine was not enough to indicate significant sugar in the urine, so that we will not speculate about it. The hemoglobin, and this is very useful to us, was not at all reduced—as though there had not been any active blood destruction. But the reticulocytes were more numerous, by a good deal, than I would expect them to be at this age. We have a series of serum bilirubin values, which are of interest, not only in that they are high, but in that in three out of four determinations the one-minute or direct bilirubin was higher than the indirect bilirubin. The baby was group O Rh-positive, Coombs negative, and seemingly could not have had erythroblastosis on a basis of blood-group incompatibility. "No erythrophagocytosis of the patient's incubated cells was found," which I think is further evidence against erythroblastosis, because I believe that if erythrophagocytosis can be demonstrated, it tends to fit in with erythroblastosis. Examinations of the parents' reticulocyte counts, which were done, I suppose, in an attempt to get some lead as to the presence of a familial acholuric jaundice in the background, tended to rule that out. We do not have any platelet count on the infant's blood or on the mother's blood, which is an unfortunate omission in terms of the conditions we have to consider.

An exchange transfusion was done fairly soon after the baby was admitted to the hospital, I suppose in an attempt to protect the infant from cerebral damage due to the elevated bilirubin. Whether this was wise or necessary, I think we might consider after we know the real cause of this infant's death. A second exchange transfusion was performed because the bilirubin rose again, and during that exchange transfusion the baby became worse and died.

This was, in summary, a small and sick baby with a hepatosplenomegaly, very early jaundice, and bleeding. I do not think she had erythroblastosis fetalis, though she died at about 2½ days of age, during an exchange transfusion. Why did she not have erythroblastosis fetalis? There was no evidence of incompatibility, the Coombs test was negative, and the icterus was almost too early, although if Dr. Gellis, Dr. Clifford, and Dr. Allen are here, we can have an argument about that. Also, the direct bilirubin was very definitely elevated quite early in the game, before there

should be any obstruction of inspissated bile in erythroblastosis. I would think, on the basis of those facts, that whatever the infant had, it was not erythroblastosis.

DR. SIDNEY FARBER.—Dr. Smith, may I interrupt? You did ask about the placenta, did you not?

DR. SMITH.—Yes.

DR. FARBER.—Tissue blocks were obtained. You might be interested in knowing that there was nothing found in the placenta that would be consistent with the diagnosis of erythroblastosis fetalis.

DR. SMITH.—Thank you. Also, I think that big placentas are not as common in erythroblastosis as they were once thought to be, so I have tended to think that the twice-normal size of the placenta would be, if anything, a little against erythroblastosis.

If this was not erythroblastosis, what was it? I have made a list of a good many possibilities, which I want to go over fairly fast. The first one mentioned is, with quotation marks around it, infection. I often think "infection" in this sense has become the "status thymicolymphaticus" of this hospital. In other hospitals, in other times, those unable to make a diagnosis could blame the thymus. We could, I think, be properly accused of settling upon unspecified infection as our "thymus," particularly in newborn babies. "Infection" is a slightly more justifiable diagnostic refuge than the "thymus," because babies do die of sepsis from various organisms, even in the midst of antimicrobial therapy. Since this baby had icterus, had bleeding, and died, I would seriously consider sepsis although icterus seldom begins so early in sepsis, and the newborn infants whom we see with sepsis seldom have this much purpura this early. I do not believe we can rule out the possibility of a staphylococcal or a *Bacterium coli* infection. Of course, any kind of infection may have come into the picture terminally, after the child became ill with something else; but that would not be my favored diagnosis here. As to specific infections, I think we can omit syphilis, on the basis of the serology of both mother and infant.

Congenital anomalies of the bile ducts, which we always think of in infants with otherwise unexplained jaundice, we pass over because bile duct anomalies are not, as a rule, associated with icterus this early, or with bleeding, or with the rapid course of this child. Then there is the inspissated bile syndrome, which Drs. Gellis, Craig, and Hsia[1] have taught us is usually a form of neonatal hepatitis. Again, in that process, the syndrome of jaundice of an obstructive nature begins later and runs a slower course, and bleeding is not present. One cannot, however, say that this infant did or did not have neonatal hepatitis without either carefully excluding every other possibility or having biopsy or autopsy knowledge of the liver.

Neither can I rule out toxoplasmosis, particularly in view of the fact that Flynn and Beckett[2] recently reported two cases of toxoplasmosis in Hartford, one of which was extremely like this baby, in having jaundice and purpura very early in life. That infant died during the first day with nothing to call attention directly to his eyes or to the neurological system, yet he turned out to have toxoplasmosis. I do not see how we could be sure

this infant did not have toxoplasmosis, with the icterus, purpura, hepatomegaly, and splenomegaly, and without blood tests, x-ray studies, or ophthalmologic examinations necessary for making a diagnosis of toxoplasmosis.

The syndrome of congenital familial, nonhemolytic jaundice, described by Crigler and Najjar,[3] I will mention only because it is always thought of in babies with jaundice. But there was no family history in this infant, and the described infants did not have hepatomegaly or splenomegaly, nor did they tend to bleed.

The diagnosis I favor is one that I learned by attending these conferences and listening to Dr. Fred Allen discuss an infant who was presented some years ago as having erythroblastosis fetalis, and only through the alertness of Mr. John Carabitses of the staff was the infant ultimately discovered to have "inclusion-body disease." The second time that baby was presented at a Pathological Conference, Dr. Allen gave a very nice discussion and stressed the infant's early jaundice and purpuric bleeding, which were very much like those of today's patient. That proved to be a case of cytomegalic inclusion-body disease with low platelet levels. We do not know about the platelets in today's baby, but I should think they may have been rather low. Most of the babies born with cytomegalic inclusion-body disease seem to be rather small, as this baby was. We do not know much about the placenta in that disease, but the peculiarity of this placenta in size might go along with some agent reaching the fetus through it. I hope that will be the diagnosis, since Dr. Farber has for many years strongly resisted the idea of cytomegalic inclusion disease as a cause of death in newborn infants and I would like to be present if he changes his mind. As other choices which I cannot exclude absolutely, I think of the possibilities of sepsis from a bacterial agent, toxoplasmosis, and neonatal hepatitis.

Though I do not know the cause of this infant's death, I have been impressed with occasional recent deaths occurring, for reasons not entirely understood, in the midst of exchange transfusions. I think one has to associate these sudden deaths with the disturbance of the infant by the exchange transfusion, and seek the connection very carefully.

DR. FARBER.—Thank you, Dr. Smith. Would we like to enlarge on the list that Dr. Clement Smith gave us, or is anyone willing to establish a preference at this time? Dr. Janeway, I heard the word infection mentioned by Dr. Smith.

DR. CHARLES A. JANEWAY.—I think this baby does have some kind of infection, but one we did not mention is generalized herpes simplex in the newborn infant. I wonder whether the experience in this hospital would indicate that to be a reasonable diagnosis.

DR. FARBER.—It does occur, but it is rare. We have had a few such babies and the picture, I suppose, could simulate this, particularly if there was some superimposed infection.

We have no record of the platelets. Would you mention why you were so interested in the platelet count, Dr. Smith?

DR. SMITH.—Only because I was trying to tie this picture up with a diagnosis that I certainly have never before made on a baby. One of the few features of fatal cytomegalic inclusion-body disease that seems fairly constant is thrombocytopenia. That would, of course, not rule out leukemia or even erythroblastosis, but it should be present in inclusion-body disease.

DR. FARBER.—Or any of the other possibilities you mentioned.

DR. SMITH.—Yes. But if the platelets were high I would have a difficult time being quite so sure of the inclusion-body possibility.

DR. FARBER.—Might I suggest, if there is such a fatal disease, that we should not expect the low platelet count to be constant. Moreover, the high nucleated red cell count would be on the basis of bone marrow involvement in some process, whether it be infectious or leukemic, and would not necessarily be a constant feature of that disease any more than it is in leukemia. One can get well-established leukemia with a normal platelet count, or high platelet count for three or four weeks, or until relapse occurs.

DR. LOUIS K. DIAMOND.—Would not a hepatoma of the liver in a young infant give rise to such a picture of large liver, bleeding, and jaundice?

DR. FARBER.—Certainly the large liver and the bleeding would be two features of that disturbance. I do not recall jaundice with a hepatoma in the very young.

DR. DIAMOND.—We have had a young infant with a necrotic neuroblastoma, metastatic to the liver, who bled into the liver and had an elevated indirect bilirubin due to the absorbed pigments.

DR. FARBER.—Yes. I think it appropriate now to ask Dr. Diamond if this is erythroblastosis fetalis.

DR. DIAMOND.—I would support Dr. Smith completely in saying that none of the diagnostic features of erythroblastosis fetalis are present, especially when one considers the fact that in erythroblastosis one does not see a direct bilirubin of this level in a child of 36 hours. That is the most impressive discrepancy in this patient compared to patients with erythroblastosis. Dr. Smith has excluded, also properly, that diagnosis on the basis of very thorough studies on the mother's and the baby's blood, which showed no isoimmunization of the mother or any evidence of blood-group incompatibility. In fact, the mother had all the Rh factors, so that she could not have been immunized against any of them, and her serum failed to produce conglutination or agglutinization of the child's blood. Tested against a panel of all sorts of cells, her serum showed no evidence of abnormal antibody production. This hyperbilirubinemia is quite unlike the hyperbilirubinemia of erythroblastosis in that little of the elevated bilirubin was indirect and that bilirubin moiety was at almost a normal level.

I would see no reason for having done an exchange transfusion at all in this case, whether or not I was actually involved in the case. It was probably done on a basis of being frightened at the level of bilirubin, not only the level at 36 hours when the child came in, but the fear that it would rise to a toxic level. We believe, in general,

that anything over 20 or 25 mg. per cent of the indirect-acting bilirubin may be damaging to the brain cells of a child of this age. An exchange transfusion was then probably done as an emergency measure immediately after the baby entered the hospital, before all this additional data about antibodies could have been obtained. If the baby was to be given blood by exchange transfusion in this particular case I do not know why it was given Rh-negative blood. It should have been given blood of the same Rh type as the mother, or blood matched up by use of the mother's serum against the donor cells. Possibly that was done, and Rh-negative blood was taken because the mother's serum failed to show an antibody reaction against it. The second exchange transfusion was done because of fear of the level of bilirubin but not necessarily because of the diagnosis of erythroblastosis. Here, it seems to be quite unjustified in that the indirect bilirubin level was not high, although the direct levels were high. The total levels were reduced by the first exchange from a total of 25 mg. per cent to a total of 11 mg. per cent and then rose again ten hours later to a total of 33 mg. per cent, of which only 15 mg. per cent was indirect bilirubin.

I, too, would have considered only the diagnostic possibilities Dr. Smith has mentioned, except that I am much impressed by this high direct bilirubin. It suggests as early as this that this child may have had intrauterine hepatic disease, and very quickly after birth, when no further help from the mother's placental elimination prevented it, an elevation of bilirubin of a direct type. Thus, some form of hepatitis of a nature such as cytomegalic inclusion disease, toxoplasmosis, or sepsis in intrauterine life might have produced this picture and gone to complete the rest of the findings given here.

The baby did not have a 25 per cent reticulocyte count according to our tests. There were 25 nucleated red cells in the first count and only 11 per cent reticulocytes. The next day, after exchange transfusion, the reticulocytes were down to 3.6 per cent. There was no evidence for congenital or hereditary spherocytosis in the baby's smear or in the mother's or father's blood.

DR. JANEWAY.—Maybe some of the people conversant with hepatic disease would know more about it than I, but I do not believe that any baby with viral hepatitis has presented with jaundice in this early life. Most of them have developed jaundice in the first few weeks after birth.

A PHYSICIAN.—Might a viral hepatitis appear in the newborn without evidence of disease in the mother?

DR. FARBER.—Dr. Janeway, will you answer that?

DR. JANEWAY.—Yes. The situation may be similar to that of blood donors who have no external evidence of disease but may transmit disease to blood recipients.

DR. WILLIAM OBER.—Clinicians are picking up milder cases of erythroblastosis fetalis, not earlier, but milder; and the placentas are likely to be small but normal. In severe erythroblastosis fetalis the placenta is large and very succulent.

A PHYSICIAN.—I would like to know the rationale behind the cortisone treatment?

DR. HAGGERTY.—I think it is becoming the custom with extremely sick, shocked babies to use cortisone. Also, this was thought perhaps to be an inspissated bile syndrome in which cortisone is used for its cholagogic effect.

DR. DIAMOND.—It is unusual to have the inspissated bile syndrome so early in life, and since Dr. Gellis has repeatedly emphasized the cholagogic effect of cortisone on jaundice in newborn babies, it is therefore logical to use it on the basis of a high direct bilirubin in infants who have hepatic disease with obstruction.

DR. FARBER.—But your studies led you to believe that there was no obstruction?

DR. DIAMOND.—There was some obstruction here on the basis of the high direct bilirubin, although this may have been at the hepatocellular level, to be sure.

DR. EDNA SOBEL.—Other reasons for using cortisone treatment were that the platelets were known to be low and the integrity of the capillary endothelium was damaged. Cortisone might have some effect on the capillary endothelium.

A PHYSICIAN.—Two outside possibilities have occurred to me. One is the congenital atresia of the hepatic vein of the liver. I think I remember seeing one such case. The other is the possibility of the mother's having had some toxin, of which she showed no clinical symptoms, that might have been passed to the infant.

DR. WILLIAM A. CHEATHAM.—The infant had the majority of the gross and histologic findings that are associated with toxoplasmosis *(Toxoplasma gondii)*. The infant was rather small, though well developed. The described nodules were ecchymoses, and a number of petechiae were also present, both on the skin surface and surface of the viscera. The heart was enlarged (29 grams; normal, 12 grams) and was the seat of a focal myocarditis with a mononuclear exudate (Fig. 1). The lungs, which were a mottled dark red color, contained much aspirated amniotic fluid debris, squamous cells, and also of bile-stained gastric content. The spleen was seven times larger than normal and its enlargement was due to a combination of congestion, erythropoiesis, and proliferation of sinusoidal reticuloendothelial cells. The liver was also enlarged and microscopically was altered by periportal fibrosis, erythropoiesis, bile duct proliferation, and marked bile stasis (Fig. 2).

The voluntary muscle had focal mononuclear infiltrations. In no areas outside the brain were organisms identified. The brain was overweight but on external examination presented no abnormality. Only after it was cut after fixation were the paraventricular and deep cortical areas of necrosis found. It was for this reason that no attempt at isolation of the organisms was made from the postmortem material. The granulomas within the brain were extensive, some early and others with calcification (Fig. 3). Both vegetative and pseudocyst forms of Toxoplasma (Fig. 4) were identified. The umbilical cord contained several pseudocyst forms (Fig. 5). The placental villi were broad and edematous. We believe, on morphologic grounds alone, that this child had toxoplasmosis. We, of

Fig. 1.

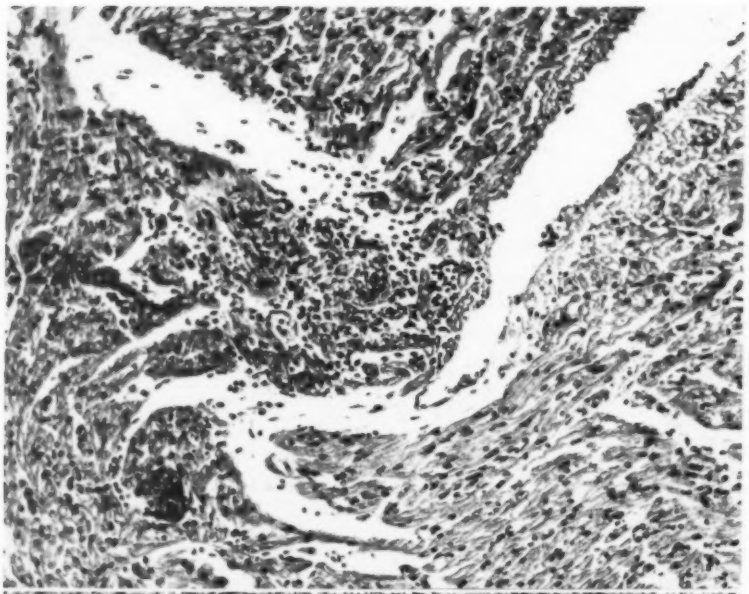


Fig. 2.

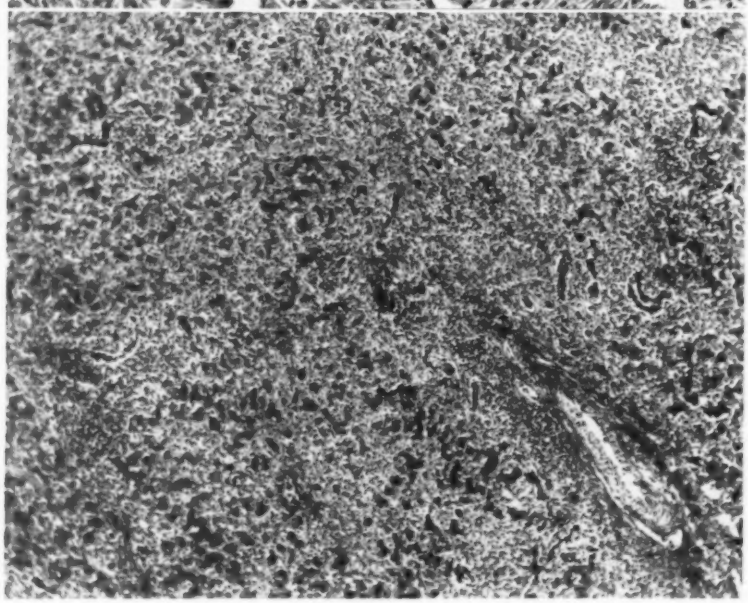
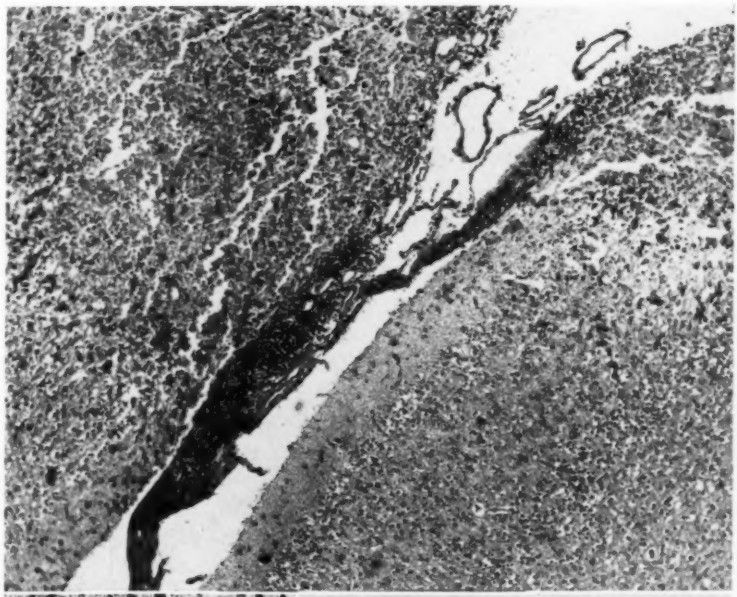


Fig. 1.—Photomicrograph, heart. A destructive inflammatory process is present in the myocardium. (Hematoxylin and eosin; ×200; reduced ⅛.)

Fig. 2.—Photomicrograph, liver. A marked destructive process with bile duct proliferation, periportal fibrosis and bile stasis is present in the liver. (Hematoxylin and eosin; ×85; reduced ⅛.)

Fig. 3.



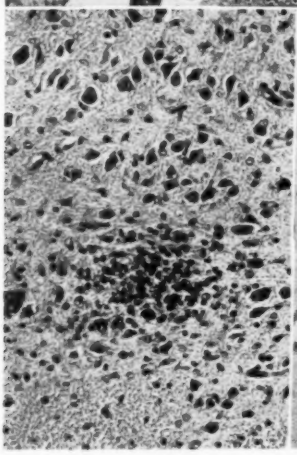


Fig. 4.

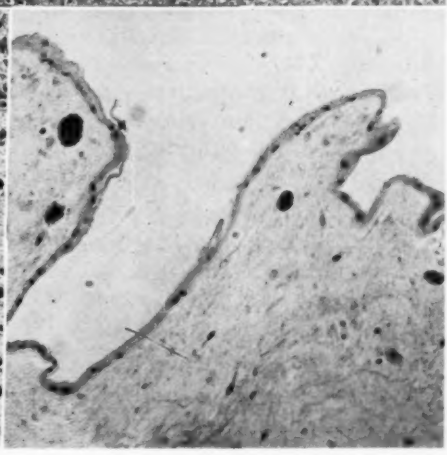


Fig. 5.

Fig. 3.—Photomicrograph, brain. One of many extensive granulomas with meningitis and calcification present in the cerebral cortex. Hematoxylin and eosin; ×95; reduced ⅛.)

Fig. 4.—Photomicrograph, brain. A small glial nodule in the midbrain with a pseudocyst. (Hematoxylin and eosin; ×280; reduced ⅛.)

Fig. 5.—Photomicrograph, umbilical cord. Four pseudocysts are present in the umbilical cord beneath the amnion layer. (Hematoxylin and eosin; ×200; reduced ⅛.)

course, would have liked to have cultural or serologic confirmation of this diagnosis.

DR. FARBER.—Thank you, Dr. Cheatham. Dr. Winter, would you like to speak on any part of this discussion?

DR. DAVID E. WINTER.—I think the only comment one can make—although there is no possibility of verifying the fact now—is that the mother's serum could have been obtained and a dye test performed. If it were negative, it would be highly improbable that the case was toxoplasmosis, as it would be unlikely for the mother's antibodies to drop so low in just two months. If it were positive, it would imply that this could perfectly well be toxoplasmosis, but it would not be absolute proof. Both mother and baby could have a high titer of dye-test antibodies resulting from maternal infection any time prior to this pregnancy, with this infant not necessarily being infected. The obvious way to make the diagnosis is by inoculation of tissue or spinal fluid into animals or tissue cultures, with isolation of the organisms.

DR. HAGGERTY.—This is the case in which Dr. Whipple, of Dartmouth, got what is properly known as a convalescent blood, and this was on the mother. The Toxoplasma dye-titer was 1:1,024 at the time of the baby's admission.

DR. WINTER.—Yes. This was analyzed only after the post-mortem examination, however. The titer certainly fits in with a chronically active infection, although such levels may be maintained for several months or years after another infection.

DR. FARBER.—I think on the basis of the morphology alone that one would have to have some very good arguments against accepting this diagnosis. Would you agree with that, Dr. Ober?

DR. OBER.—Yes, I would like to know if toxoplasmosis was identified in the liver?

DR. CHEATHAM.—No.

DR. FARBER.—That is a question of luck and a prolonged search through many sections of liver.

I believe Dr. Clement Smith made the point that he could not exclude toxoplasmosis with this story. Before turning the discussion back to Dr. Smith I would like to make one comment about the clinical picture of disseminated cytomegalic inclusion disease. The reference that Dr. Smith made to the cytomegalic inclusion-body disease concerns the objection I still have, which is the establishment of a clean-cut clinical disease entity, associated with a given etiological factor at any age period. When one is dealing with a disseminated disease, which may or may not involve the brain, the heart, the liver, the spleen, or the bone marrow, in any given case, but not necessarily all of them, I think it is worth while emphasizing that we are dealing with a variable picture; toxoplasmosis itself is a beautiful example.

In the first case of toxoplasmosis we had here,[4] we found only the heart involved. Later on, in that same case, Toxoplasma was found in the brain and in other organs, but only after prolonged search. The disease turned out to be much more widespread than we had first realized. The disease was first well described and recognized by Wolfe and Cowen,[5] because of a case with involvement of the brain. The brain involvement may vary greatly.

In the case of inclusion-body disease, I still have certain reservations concerning the relationship of some of the organ changes to the actual agent, and I would like to keep those reservations until we have a little more evidence. All in all, I would say the best that one can do with a problem of this kind is to phrase it as Dr. Smith did; then one cannot exclude toxoplasmosis. If one can reach that conclusion during life, there would be certain things that could be done immediately to establish the diagnosis. In a case of toxoplasmosis, of course, energetic attempts at therapy might be tried and might be of value if the brain damage is not too great. So we are dealing with an entity that is no longer merely a diagnostic problem, but is one that is in the field of therapy.

Dr. Winter, would you say a word about that?

DR. WINTER.—The damage is usually well advanced by the time a diagnosis can be established, so that even if therapy resulted in cure of the infection, the baby would be severely affected. In experimental animals a number of therapeutic agents are utilized. The sulfonamides are one group that do quite well. Others are experimental compounds that include Daraprim, Puromycin, and some of the dihydrotriazines. A combination of some of these drugs with sulfonamides may turn out to be helpful.

DR. FARBER.—What hope is there of establishing the diagnosis during pregnancy?

DR. WINTER.—I think only by more or less blindly taking sera for dye tests and detecting a rise in titer in someone who has no antibodies at the onset of pregnancy, can we recognize cases in pregnancy for treatment.

DR. ALWIN M. PAPPENHEIMER.†—Dr. Cheatham has presented a beautiful demonstration of Toxoplasma in the umbilical cord. Is that a new observation or has that been seen before? Could that be used as a diagnostic test?

DR. CHEATHAM.—I do not know about the umbilical cord, but there are at least three cases in which Toxoplasma has been identified in the placenta.

DR. FARBER.—Ideally, we should begin treatment quite a time before delivery, before the damage has reached the point that we see it in the brain. If there is going to be any possibility of effective therapy, it will have to be done during pregnancy. I think that that offers a challenge for those in maternity hospitals to establish a diagnosis early and to treat the mother with the sulfonamides or dihydrotriazine, or the antimalarial Daraprim, or Puromycin, which is an antibiotic. The last mentioned is of great interest because it is effective, at least in laboratory animals, against amebic dysentery to a greater degree than any other antibiotic.

Dr. Smith, would you like to conclude?

DR. SMITH.—I think that, given the same information again, I would go through the same line of thought. I appreciate the point that you have been bringing out, namely, the help that one could get in establishing a correct diagnosis in such a brief lifetime as this baby had. I think that

†Deceased.

in women who have had one child with toxoplasmosis—and it might be true of the people who have not had a child with toxoplasmosis—the titer may rise during pregnancy, without the child being affected. So, I think the mere fact of a rising titer in the dye test during pregnancy would still not be entirely conclusive.

DR. WINTER.—I implied the appearance of a titer in a woman with no titer at the start of pregnancy.

DR. SMITH.—Yes; if it started with nothing at all. But a good many women have some titer. If the woman already had a demonstrable titer then we would get nowhere.

DR. JANEWAY.—Is it not true, Dr. Farber, that if one found a positive dye test in a woman, early in pregnancy, one could rest completely assured that the baby would not get toxoplasmosis? These affected babies are invariably babies born to mothers who have acquired the infection in the course of the pregnancy.

DR. WINTER.—Stanton and Pinkerton[6] reported a case of a woman who, forty-three weeks after clinical toxoplasmosis, diagnosed by biopsy of a lymph node, had a normal infant in whom a high passive titer could be demonstrated in which the antibodies had presumably been passed across the placenta to the infant.

DR. FARBER.—One final question, Dr. Winter. Do you have figures on the incidence of the infection and the incidence of the disease?

DR. WINTER.—I think all one can say about that is that by the third or fourth decade in various cities about half the population have antibodies. The clinical disease is rare and manifests itself as infectious mononucleosis or something else.

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Medical Progress

THORACIC NEUROBLASTOMA

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WASHINGTON, D.C.

PRIMARY location of a neuroblastoma in the thoracic cavity is not common. I have been able to find seventy-nine cases reported in the English literature.[1-46] In order to gather this number, over 300 articles on neuroblastoma, thoracic tumors, mediastinal tumors, and spinal cord tumors in children[20] and textbooks on pathology and pediatrics have been reviewed.[47, 57] In addition, I wish to present a case of an infant treated personally, this bringing the total to eighty cases. Certain cases in the literature have been reported by more than one author.[4, 5, 12, 29, 1, 15, 31]

HISTORY[3, 9, 22, 45, 54, 58-62]

These tumors were originally called sarcomas or round-cell sarcoma. Virchow in 1864 suspected that they might be of nerve tissue origin and called them "glioma." Dalton in 1885 described a case of adrenal tumor with liver metastases in an infant. He was the first to consider the tumor primary in the adrenal and also to describe "rosette" formation in the tissue examined. Marchand in 1891 made the observation that certain adrenal tumors histologically resembled embryonic sympathetic nerve tissue.

Pepper in 1901 wrote a paper on congenital sarcoma of the liver and adrenals. It would appear that Pepper considered the tumors to be primary in both sites and presented them as a "special type of congenital malignant disease." Later the Pepper syndrome was applied to a "peculiar" type of adrenal neuroblastoma which manifested itself by extensive metastases to the liver.

Hutchinson in 1907 reported ten cases of what he considered to be a unique syndrome. Illness was ushered in by swelling of the eye; signs of increased intracranial pressure associated with proptosis of the affected orbit soon appeared. After a short illness, all patients died and all had a "sarcoma of the adrenal gland" with extensive metastases. In only five patients could an abdominal mass be palpated during life.

Wright in 1910 made an important contribution when he definitely stated that the cells of the tumor had the same morphology as the forerunners of the sympathetic system and the adrenal medulla. He suggested the term "neuroblastoma" for this tumor and pointed out that such tumors may arise in any location where sympathetic tissue is found. With time it has become apparent that the "Pepper syndrome" and the "Hutchinson syndrome" were mere variations in the course of the neuroblastoma.

PATHOLOGY[1, 17, 20, 31, 32, 39, 41, 43, 45, 54, 61-66]

Primitive neural cells (sympathogonia) migrate from the neural crest to

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comprise the sympathetic system and adrenal medulla. Two basic cells evolve chromaffin and ganglion cells. Various types of tumors are possible. The chromaffin cells may give rise to pheochromocytoma or paraganglioma. The ganglion cells in turn may develop into ganglioneuroma or neuroblastoma. Neuroblastoma may occur anywhere that sympathetic tissue is found. The most common sites are adrenal and periadrenal areas. Cases have been reported as occurring in all areas of the sympathetic chain (cervical to pelvic regions), jejunum, mesentery of the small bowel, liver, uterus, skin, and scapular region.

On gross examination, the thoracic neuroblastoma is a lobular mass. It is often adherent to ribs, vertebral column, or lungs. It is usually posterior mediastinal in position. Areas of hemorrhage, necrosis, and/or calcification are common.

On microscopic examination, there is no difference in thoracic neuroblastoma from cases of neuroblastoma found in other locations. The slide may have a homogenous appearance, or be mixed with the elements of a neurofibroma. When a uniform process is present, the cells are described as very small, with hyperchromatic nuclei. The cells are clumped together with little fibrous stroma; hence, the reason for early confusion with round-cell sarcoma or lymphosarcoma. Mitotic figures are abundant. Rosette formation was at one time considered characteristic of the tumor. Apparently it is found in the more mature forms. Rosette formation has been described by Askin and Geshickter as "circular arrangement of cells with cell processes extending toward a center of the circle." Areas of the more mature tumors show larger cells with abundant cytoplasm. Fibrous stroma separate groups of cells. Some fibers may stain as nerve fibers.

CLINICAL BEHAVIOR OF NEUROBLASTOMAS[11, 16, 22, 23, 31, 65, 67-69]

The behavior of neuroblastomas, in general, is that of a rapidly progressing malignancy. However, this group presents enough cases of bizarre behavior to make for fascinating reading. In evaluating various forms of treatment, such bizarre behavior must be considered.

Cases of spontaneous regression of the tumor have been reported.[55] Recovery after multiple bone metastases has been asserted.[4] Cushing has described a famous case which seemingly matured into a benign ganglioneuroma. Similar transformations from a malignant tumor have been reported by Farber. The latter author also reports cases where the tumor disappeared after simple biopsy or treatment with irradiation despite multiple metastases.

Both Gross and Koop found that neuroblastoma (thoracic location or otherwise) discovered before the age of 2 had a better prognosis than when discovered in an older child.

AGE AND SEX INCIDENCE

The sex was stated in fifty-one cases; thirty-seven patients were male. Ages varied between those of a stillborn infant[32] and a man 68 years of age.[29] Twenty-nine patients were reported to be 5 years of age or younger; ten were 6 to 10 years of age; 15 were over 10 years. In three instances the condition could be considered to be present at birth, one patient being stillborn.[32] The other two died at 4 weeks of age.[19, 25]

SYMPTOMS

The incidence of paralysis, due to extradural extension of tumor, as an initial symptom was both unexpected and impressive. The fever noted was of an unusual variety. Swinging daily curves well over 103° F. were common. In certain instances, such fever curves instituted diagnostic study and resulted in the diagnosis of a thoracic tumor. Chest pain, dyspnea, cough, and weight loss were common, as might be expected. In three patients, an asymptomatic mediastinal mass was noted on routine x-ray examination of the chest.

TABLE I. SYMPTOMS

Partial or complete paralysis of the lower extremities	18
Fever	13
Chest pain	9
Dyspnea	9
Cough	6
Weight loss or inability to gain	5
Back pain	3
Abdominal distention	3
Joint pain	2
Vomiting	2
Abdominal pain	1
Wheeze	1
Cyanosis	1
Dysphagia	1
None	3

PHYSICAL SIGNS

The neurological signs ranged from loss of sensation to paraplegia. Physical examination revealed abnormal findings in certain patients who offered no neurological complaint. The prominence of neurological signs is the more impressive when one realizes that some reviews gave little or no history of them. A number of cases are listed as pathological diagnoses only in articles dealing with thoracic tumors.

TABLE II. PHYSICAL SIGNS

Neurological signs	20
Dullness to percussion	9
Cervical and/or axillary nodes	4
Paravertebral mass	2
Proptosis of eyes	2
Palpable liver	1
Superior vena cava syndrome	1

LOCATION OF TUMOR

Table III reveals position of the tumor. The tumor more commonly projected into the right hemithorax. Unless otherwise noted, a posterior position is implied. "Middle mediastinum" is a term used by two authors. An extradural component (dumbbell tumor) was specifically described in twenty-eight cases and denied in fourteen.

TABLE III. LOCATION OF TUMOR

Superior mediastinum	
Right	16
Left	11
Inferior mediastinum	
Right	8
Left	3
Anterior mediastinum	3
Bilateral extension	3
"Middle mediastinum"	2
Entire left hemithorax	1

ASSOCIATED ANOMALIES AND/OR DISEASE

Erosion of ribs and vertebras was due to local extension of disease. The case of multiple primary sites was reported by Potter and is most interesting. The patient was a hydrocephalic stillborn infant. At autopsy, both sympathetic chains of ganglions were involved "in an almost continuous mass of tumor tissue from cervical to

TABLE IV. ASSOCIATED ANOMALIES AND/OR DISEASE

Erosion of ribs and/or vertebras	13
Multiple primary sites	1
Hydrocephalus	1
Hemophilus influenzae septicemia	1
Postvaccinal encephalitis and myelitis	1
Arachnoid cyst	1
Cardiac disease (acquired)	1
Congenital glaucoma	1
Lobar pneumonia	1
Sebaceous cyst	1

sacral areas.'' There were also bilateral adrenal neuroblastomas with metastases to the abdominal cavity. Influenzal septicemia[37] and pneumonia[3] were the cause of death in these respective cases.

TREATMENT OF NEUROBLASTOMA[16, 22, 23, 31, 65, 68-75]

Preoperative Irradiation.—Such therapy has not been used by most authors. Gross states that he has used it with encouraging results in two cases of thoracic neuroblastoma.

Surgery.—This is recognized as the only definitive therapy. It should be performed in the presence of distant metastases.[31] The primary mass should be removed as completely as possible. As Gross points out, if nothing else is accomplished, it reduces the bulk of tumor remaining for irradiation. Koop and associates found that removing as much tumor as possible improved the prognosis. For example with neuroblastoma in general, if only a biopsy was performed, the survival rate was 13 per cent; if as much tumor as possible was removed (even with distant metastases), there was a survival rate of 63 per cent. In other words, they believe that there is a correlation between ''major surgical insult'' to the tumor and ultimate survival of the patient.

Postoperative Irradiation.—Most authors feel that postoperative irradiation is strongly indicated. As Gross points out, some tumor must be left behind after surgery. At the Children's Medical Center in Boston, irradiation is started the day after surgery. A second course is given three months later. If a wide field of irradiation is necessary (abdomen and mediastinum), bone marrow must be carefully checked. Wittenberg and Keegan and co-workers have reported cases where irradiation was used following biopsy or incomplete removal of the tumor and a long-time survival followed.

Probably the lone dissenting note as regards postoperative irradiation comes from Children's Hospital in Philadelphia. Koop and associates believe that certain of these tumors normally regress or mature into a benign form. If irradiation is used, credit is given to such therapy for a course that would have occurred spontaneously. To illustrate this point they cite twelve cases in which there had been incomplete removal of the tumor. Irradiation was used inadequately for the extensive amount of malignant tissue left behind (two patients), or not at all because of a seemingly hopeless situation (ten patients). All are alive more than fourteen months following surgery. It is interesting to note that the case of longest survival, namely fifteen years, reported by Lehman, did not have irradiation therapy. At the time of the progress report, the patient was living and well.

Chemotherapy.—Chemotherapy has recently been used in the treatment of the general group of neuroblastoma. Usually the chemotherapeutic agent is used after a course of irradiation. However, Phillips has described combining nitrogen mustard with radiation.

Farber in 1951 presented a report on the largest group treated with chemotherapy. The group numbered fifty-two cases of neuroblastoma at various sites. All cases had metastasized. All patients had responded poorly to irradiation. Thirty-nine had died at the time of report. However, eight of these had had a temporary remission, and an additional nine had showed some response to treatment.

The remaining thirteen patients were alive at the time of report. Nine of these had shown regression of skeletal metastases. Agents used included nitrogen mustard, folic acid antagonists, triethylene melamine. In certain instances, cortisone was used concomitantly.

In conclusion, one might say that the treatment of neuroblastoma in general, and of the thoracic variety in particular, is surgical excision. Excision of the mass in so far as possible should be performed. Simple biopsy, even in the face of an extensive tumor or metastases, should not be the only surgery. Postoperative irradiation should be started as soon as definitive pathological diagnosis is made. If the response to x-ray is poor or recurrence occurs, chemotherapy should be employed.

RESULTS

In considering results, one must remember that many cases are merely listed in reviews of mediastinal tumors. Details of therapy are often meager. In the literature, twenty-six patients with thoracic neuroblastoma are reported as living at the time of the report. Eight patients were reported shortly after surgery.[8, 10, 16-18, 38, 46] Most of these eight patients had incomplete removal of the tumor or known metastases at the time of surgery.

Of the living patients, six had had some form of surgery only and survived for six months,[7, 35] twenty-one months,[2] twenty-seven months,[22] thirty months,[24] and nine years.[16] In this group, laminectomy was the surgery performed in one,[35] and the 9-year-old child had biopsy only.[16]

Eight had surgery plus radiation therapy and six are alive between two and three years postoperatively,[16] one at eleven months,[26] and one at twelve months.[41] Seven of these eight[16, 41] were stated to have had incomplete removal of tumor. The final patient had a biopsy, Coley's toxin, and a late laminectomy and was reported well ten years after laminectomy.[11]

In an attempt to elucidate the problem, cases studied were made of patients who had lived twelve months or more following treatment and then succumbed. There were seven such cases. One had surgery only and lived four and one-half years.[36] Another had surgery plus x-rays and lived two and one-half years.[1] One patient had a biopsy of the mass, followed by irradiation and by a laminectomy at a later date. This patient lived one year.[9] Four patients had a laminectomy for the extradural component of tumor and irradiation.[35, 42] These patients lived between one and five years.

It is most difficult to draw definite conclusions concerning treatment for a tumor when biopsy alone gives survival of nine years. In contrast, with surgery and x-ray the best survival is two-plus years. The only conclusion which I can draw is to lend credence to Koop's theory that the "surgical insult" is important.

CASE REPORT

V. B., a 6-month-old Negro female, was admitted to Children's Hospital on August 6, 1955. The mother gave a history of a two-day illness with temperature up to 104° F., dyspnea, and anorexia. The infant was treated by the family physician, who x-rayed the infant, told the mother that the patient had pneumonia, and administered penicillin. On the day of admission the infant began to have generalized convulsions. On physical examination, the temperature was 106° F. (R), pulse 140, and respiratory rate 50. There was bilateral otitis media. Examination of the thorax revealed

decreased breath sounds over the left upper lobe posteriorly with a flat percussion note. Hemoglobin was 9.7 grams, white blood count was 12,400. The admitting diagnosis was otitis media and left lobar pneumonia. The infant was treated with penicillin and Aehromycin, Croupette, aspirin, and alcohol sponges.

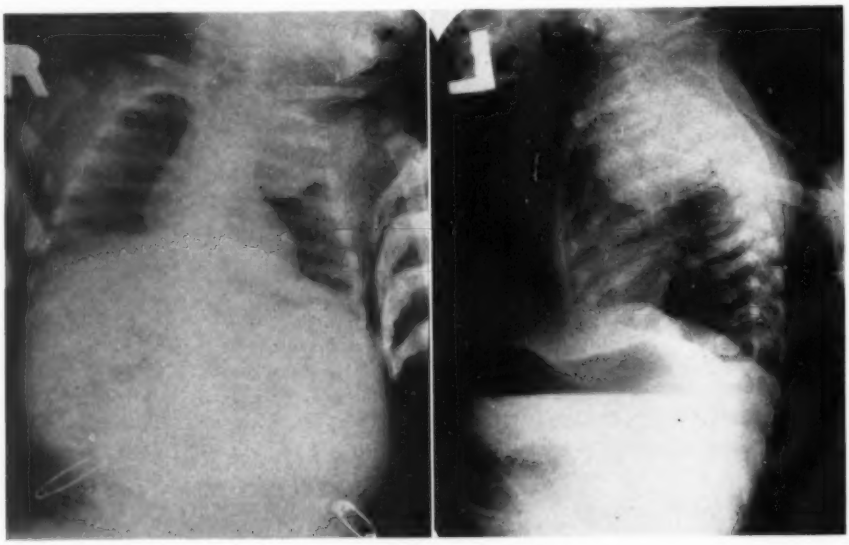

Fig. 1.—Preoperative chest film.

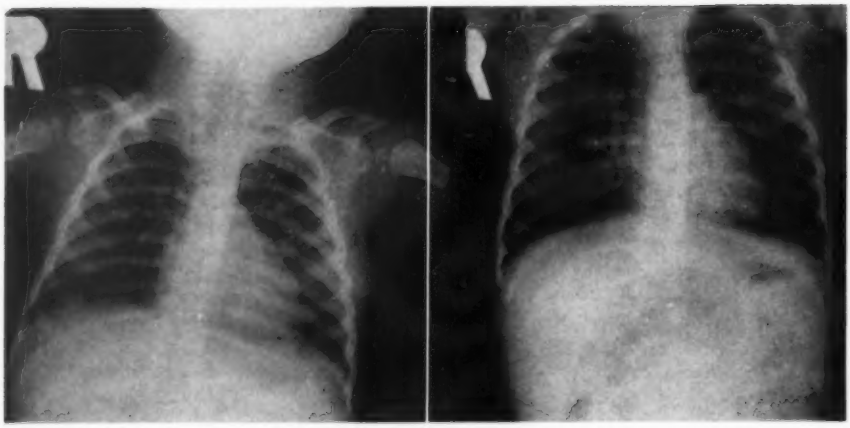

Fig. 2.—Postoperative chest films. *A*, One week after surgery. *B*, One week before death.

On the following day, the infant appeared more comfortable. The temperature was normal. There was no dyspnea, and the patient took her formula well. Abdominal distention was noted. No chest film had been made after that done by the private physician, and the patient seemed to be progressing well.

On the third day of admission, the infant appeared very irritable; the temperature was elevated. Nuchal rigidity and abdominal distention were

present. A spinal tap revealed 700 mg. per cent protein, 63 mg. per cent sugar, and 2 white blood cells. The following day, dribbling of urine was noted. Catheterization was performed, 400 c.c. of urine obtained, and the abdominal distention disappeared. A chest film revealed a round mass in the upper portion of the left hemithorax; the trachea was displaced to the right. The impression of the radiologist was that the mass represented a neuroblastoma or teratoma. Radiographic study of the skull and long bones was negative. Intravenous pyelogram showed normal kidneys. On cystogram, there was atonia of the bladder; the latter contained 300 c.c. of radiopaque dye.

The following day, the infant was seen by neurosurgical and thoracic surgical consultants. The former noted paraplegia with anesthesia to the level of T_2. The cranial nerves were intact. There was bilateral ankle clonus, diminished tendon reflexes. A myelogram showed obstruction at T_2. The opinion was that the infant had a benign neurogenic tumor of the thorax, with extradural extensions. The extradural component was deemed the more urgent.

On August 15, a laminectomy was performed by Dr. Johnathan Williams. An encapsulated extradural tumor was encountered. The mass projected from the second intervertebral foramen. The mass was dark red and was removed. The pathological report was benign embryonal neurogenic tumor.

The postlaminectomy course was marked by a septic fever curve. Rectal temperatures up to 105° F. and 107° F. were noted, and several episodes of severe dyspnea occurred. On August 20 a left thoracotomy was performed. The upper lobe was compressed by a tumor of golf-ball size. In some areas the mass was grayish white, in other areas, purplish red. The tumor was extrapleural, appeared well encapsulated and appeared to arise from the thoracic sympathetic chain. The mass was removed in toto, including a projection into the second vertebral foramen. The chest cavity was drained. Again the postoperative course was stormy. Temperature of 107° F. (R) was noted on the night of surgery. Irregular temperature continued. Abdominal distention was a stubborn problem. The left lung was completely expanded on the first postoperative day. There was never any evidence of pulmonary or wound complications.

The microscopic diagnosis of the thoracic mass was neuroblastoma. Repeat radiographic study of the skull, chest, and long bones was negative. Bone marrow aspiration was negative for malignant cells.

Irradiation therapy was started on Aug. 23, 1955. The plan was to give 4,000 r at the rate of 100 r per day. Actually, daily therapy was stopped on Sept. 26, 1955, because of a white blood count of 2,000. Total dosage to that date had been 2,208 r. Chemotherapy in the form of 6-mercaptopurine was started on a dosage of 25 mg. daily from Aug. 23, to Sept. 25, 1955. From the latter date to Oct. 7, 1955, it was given every other day and then stopped.

During the post-thoracotomy period, because of irregular temperature and urinary infection (*Micrococcus pyogenes* and beta hemolytic streptococcus), various antibiotics were used: penicillin, penicillin combined with streptomycin, the tetracycline group.

Clinically, during the most of September the infant seemed to improve. Despite the temperature curve, the infant did not appear ill. On September 25, a routine blood count revealed 2,000 white blood cells. Antibiotics were restarted.

On October 1, the infant began to appear ill. Physical examination suggested left pneumonia. The chest film appeared normal. The temperature curve continued septic, as before. The infant became irritable, then lethargic and refused to eat. Blood cultures were negative. Various antibiotics were used and made no change. The infant died on Oct. 21, 1955.

At autopsy, there was a necrotizing pneumonia of the left lung, pleural effusion of 20 c.c. on the left, and

aplasia of bone marrow. There was no evidence of tumor in the thorax, but a recurrence or persistence was noted in the spinal column. Here a flat extradural mass extended from T_2 to T_9. There was no compression of the spinal cord. Culture of the heart blood and left pleural field revealed *Escherichia coli*.

SUMMARY

Primary location of a neuroblastoma in the thoracic cavity is not common. Eighty such cases are reviewed. A high incidence of neurological disturbances secondary to extradural extension of the tumor was noted. Previous literature has not stressed such incidence. Fever is also a common finding.

The condition is more common in males of 5 years of age or younger. The tumor is usually located in the posterior mediastinum and projects into the right hemithorax.

Surgery is the basic treatment. The primary tumor should be excised as completely as possible, even in the presence of distant metastases.

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Pediatric Profiles

John Hall Mason Knox, Jr.

(1872-1951)

THE contributions of J. H. Mason Knox, Jr., were in public health rather than in clinical or scientific pediatrics. He began to assume responsibility for the health of mothers and children shortly after completing his hospital training and continued, as he himself wrote, until "we grew old in the service." His first solid effort and success was directed at providing safe milk to infants of low income families in Baltimore. This activity brought him into contact with individuals and organizations in this and other countries that were concerned with the enormous infant mortality rates which prevailed at the turn of the century. These developing interests and friendships led him to be one of the founders and first president of the American Association for the Study and Prevention of Infant Mortality and finally to devote his full time to this work.

It is perhaps easier to assess the contributions of a scientist in medicine than of one whose work is in public health. The work of the former may be based on the earlier efforts of many others but it is usually possible to know which individuals have brought a long line of endeavor to a successful conclusion. Great advances in the prevention of illness are less clearly attributable to any one individual; they usually depend on the combined efforts of many persons from various disciplines in voluntary and public agencies and ultimately on the enlightened self-interest of every responsible individual. It was the application of the new knowledge of bacteriology by this latter type of effort which was chiefly responsible for the great drop in mortality that occurred in the first third of this century.

Knox's share in this activity does not appear to have been planned. He was born in 1872 in Philadelphia and spent his early years there. He attended high school and began college in Easton, Pennsylvania, where his father, the Rev. J. H. M. Knox, was President of Lafayette College. He was graduated from Yale in 1892 and continued on for a Ph.D. in physiological chemistry under the late Professor Lafayette B. Mendel. He received a degree in medicine from Johns Hopkins in 1898 and after an internship entered private practice in Baltimore in 1900.

In that same year, he spent part of the summer as one of the volunteer physicians for the Thomas Wilson Sanitarium which had been established "for the purpose of securing a summer retreat for sick children from the heat and unhealthfulness of the city" of Baltimore. Knox so impressed the trustees that they offered him the post of part-time medical director at an annual salary of $750. He hesitated and wrote, "my absence last summer for so long seriously impaired the little practice I had attended to in the spring," then accepted the offer and continued in this post until 1921. Over the years, he gradually influenced the trustees of this foundation to give more and more of their income to the Babies Milk Fund to provide a safe milk supply and also to support an early type of visiting nurse service.

Knox had the idea of making this sanitarium a center for research and teaching about diarrheal diseases of children. He recruited young Hopkins graduates for the staff, obtained funds for a pathologist, and always took great pride in the fact that the Flexner type of dysentery bacillus previously described in Japan, and then in prison populations in this country, was first discovered in the stools of infants with "summer complaint" at the Thomas Wilson Sanitarium.* Knox's part in this appears to have been that of encouragement and obtaining funds; there is no evidence that he took an active part in the studies and there is no record of any continuing research.

At the end of his first summer as medical director he asked the trustees for leave with pay to go to Europe for study until February. There are subsequent notes in the minutes that the opening or closing of the Sanitarium was sometimes delayed or accelerated by a week or two so that Dr. Knox could attend some medical meeting at home or abroad.

He was one of that small but informed group who attended the Yale Conference on the Prevention of Infant Mortality in November, 1909, and organized The American Association for Study and Prevention of Infant Mortality, with Knox as its first president.

The first annual meeting of this new Association in Baltimore in 1910 was carefully planned and eminently successful in focusing public interest on the problems of excessive mortality in infants and children. The list of speakers attested to Knox's appreciation of the variety of interests that must be brought to work together. The Chief Statistician of the Federal Bureau of the Census talked on the same program with Drs. Abraham Jacobi, Irving Fisher,

*Duval, C. W., and Bassett, V. H.: Etiology of Summer Diarrhea in Infants, Am. Med, 4: 417, 1902.

and William H. Welch. Wide publicity in the fine sense was assured by the presence of Cardinal Gibbons and the then greatly beloved Ambassador from France, Hon. Jules Jusserand, who gave the principal address. A large educational exhibit, the first of its kind in this country, presented graphic data about infant mortality and its prevention through proper feeding and care.

The secretary, treasurer, and executive offices of this Association were located in Baltimore for the next twelve years and during this time, Knox carried a large part of the burden of making it a forceful and effective agency. It was renamed the American Child Hygiene Association in 1918 and merged with the American Child Health Association in 1922. These organizations, together with the United States Children's Bureau, gave a national focus and impetus to the child health movement during these years. The published transactions are "year books of progress in Child Health" and a Who's Who of pioneer workers in this field. Drs. Martha Eliot and Grover Powers have told me that they consider this work to have been one of Knox's major contributions.

At the same time Knox developed a large private practice and became actively associated with many voluntary organizations devoted to the interests of children, and eventually was a member of the board of a surprising number of such agencies. These years also brought one of his great disappointments, when he was passed over for the professorship of pediatrics at Hopkins, a post which even his greatest admirers felt was outside his field of deepest interest and competence.

He was one of the first prominent pediatricians in this country to devote himself full time to public health. The shift from private practice began in 1917 when he served in the American Red Cross as Associate Chief, Children's Bureau, Department of Civil Affairs, Paris, France. This organization supplied nursing medical supervision to the war-stricken children of France. A number of colonies for orphaned children and several health centers and hospitals were established. Contributions through the Bureau resulted in the establishment of the École de Pueri culture, later a part of the University of Paris. After the war, Knox returned briefly to private practice, but in 1921 he again returned to Europe as field medical director of the child health work carried on by the American Red Cross in Central Europe.

In 1922 he became head of the Bureau of Child Hygiene in the Maryland State Department of Health and continued in this post until his retirement in 1942. The development of this Bureau paralled similar work in other states, but Knox made several contributions which, if not entirely original, were pioneer projects in that time and have endured.

One was the initiation of a state-wide pediatric consultant service with full-time pediatricians, the initial incumbent being Dr. Myron Wegman. The current pediatric consultation clinics which are held at frequent intervals in most sections of the State grew from these early beginnings. These clinics provide consultation service to children referred by well-child conferences, school health services, and private physicians. Patients who need more careful investigation than that

given by this itinerant type of consultation are referred to one of the teaching hospitals for further study. This service has brought and still brings skilled diagnostic care to children who, because of geographic or economic status, have need of such assistance.

The obstetric consultation clinics provide a similar service to pregnant women throughout the State and have a similar history. These clinics and the public prenatal clinics serve the lowest socioeconomic segment of the population; yet the race specific maternal mortality has been lower in this group of patients than in the general population of Maryland.*

Child Guidance Clinics usually under voluntary auspices were operating in many cities by the early thirties. Knox determined to make similar services available in the rural areas of Maryland. This he did by obtaining the volunteer services of Dr. Esther Richards and other psychiatrists and by using health department personnel to do the staff work for occasional clinics throughout the State. These early efforts made it easy for the State Health Department to establish a Bureau of Mental Hygiene with a state-wide system of clinics after World War II.

Knox first proposed to the U. S. Children's Bureau that Federal funds be used for a maternal and child health demonstration program in Ann Arundel County, Maryland, and so was instrumental in the development of such projects in various parts of the country.†

I have talked or corresponded with many of the nurses, obstetricians, pediatricians, and others who worked with Dr. Knox in the Bureau of Child Hygiene; the consensus is well expressed by one who wrote, "I left Maryland feeling that I had been able to do a fairly good piece of work for the Health Department, but I am perfectly sure that it never would have been possible without the guidance, leadership, and inspiration of Dr. Knox."

Not all of the innovations introduced by Knox had smooth sailing. He had a way of quietly moving the Health Department into service programs which sometimes led to controversy that was disturbing to his superiors. When the State Board of Health found it necessary to curtail a new Knoxian service, he accepted the verdict with reasonable good grace. But, so far as I have discovered, he never voluntarily retreated from a course which seemed to him to fill a real need.

Knox, like many other pioneers, combined ideas and activities which were considered liberal and even radical with other points of view which were conservative and reactionary. Thus, his early avowed objective was to so develop the work of the Babies Milk Fund that it would be taken over as a public service. But when the time arrived, he imposed repeated delays until it was necessary to obtain a survey by an eminent outside health authority to convince him that a change to Health Department auspices could safely be made.

The influence of a strict Presbyterian family background was seen throughout his life. The first available evidence of this is in his many letters to former college classmates which continued almost to the end

*Whitridge, John, Jr., and Davens, E.: Are Public Health Maternity Programs Effective and Necessary, Am. J. Pub. Health 42: 508, 1952.

†Dr. Martha Eliot: Personal communication.

of his career. Most of these letters were to or about friends who had become missionaries or entered the ministry. He kept up with the work, change of residence, and successes of a surprising number of these early classmates. Knox, himself, always took an active and prominent part in the affairs of the First Presbyterian Church of Baltimore.

There was a slow stubbornness and persistence about Knox that had much to do with his accomplishments. He let it be known early in his years of practice that he would be glad to see children who were well, to advise about their feeding and to give general health supervision. The idea of inviting visits from well children and charging for this was then so unorthodox that there was considerable and outspoken sentiment to expel him from the medical society.* The matter never assumed importance. But it is pertinent that Knox quietly laid the foundations which forty years later resulted in Maryland placing second among the states in child health conference work.†

Knox became a member of the American Pediatric Society in 1904 and president in 1925. At one meeting in the twenties, a late afternoon swimming party was planned, to be followed by a chartered bus ride to a noted restaurant. Knox appeared at the swimming pool, smoking one of his favorite stogies, wearing a stiff straw hat and a long black bathing suit that was unanimously voted the best 1890 model on the scene. The fact that the punch was heavily laden with champagne was carefully kept from Knox who was a strict observer of the Eighteenth Amendment. He found it good and was encouraged, especially by the ladies, to have several glasses, so that he became quite gay and even mildly boisterous.

Under a somewhat dour and severe exterior Knox had an interest in people. He knew the birthdays and other major events in the lives of all employees of his Bureau and always remembered them with some little gift or greeting. He continually traveled around Maryland, calling on physicians, health department personnel, and anyone else who was interested or could be influential in maternal and child health work. He knew about crops, the weather, and local matters, and had a knack of being on friendly terms with many private practitioners. Many clinics in the rural parts of the state required an overnight trip and Knox was frequently the guest of a local practitioner; in return he provided a sort of armchair consultation and invited his host to the morrow's clinic.

He kept a careful file of his correspondence and other papers. This is filled with letters on all sorts of subjects to a great variety of individuals. There are several letters about a street in Alexandria, Virginia, which derived its name by a fairly direct but long-forgotten route from a monastery in Scotland. There is a letter to the then President of Vassar College, hoping that he can reassure a friend who is also the parent of a prospective student about some aspects of the curriculum. There are letters to former employees of the

*Dr. Huntington Williams: Personal communication.

†American Academy of Pediatrics: Survey of Child Health Services, The Commonwealth Fund, 1949.

health department inquiring about their health and telling of changes which would be of interest.

Knox was a member of the Bachelor's Cotillion in Baltimore and occasionally wrote to recommend for presentation the debutante daughter of some old friend or associate in child health work. There was nothing equivocal about such letters which were an occasion for "pulling out all the stops."

A large part of his correspondence was to or about members of his family. Dr. and Mrs. Knox had five children and his many letters to and about them indicate interest in their activities and a restrained pride in their accomplishments. The file has scores of poems written and read by Knox at a birthday or other anniversary celebration and on other more general subjects. These rhymed lines were evidence of his effort to add his bit to these events.

His chief recreations were tennis, fly-fishing, and bridge. A foursome met every Saturday afternoon at his house for tennis, or, in poor weather, for bridge. Knox played tennis regularly until well past seventy.

I met Dr. Knox about the time of my appointment as the first full-time head of the Division of Maternal and Child Health in the Johns Hopkins School of Hygiene and Public Health. He told me that he had given the first course at Hopkins on this subject and offered his services. A few weeks later, he telephoned that there was a meeting to which I should go and would I like to ride with him. These rides became frequent and were of some interest to our mutual acquaintances. It appeared that Knox had a reputation for being an erratic driver and for liking company. Once, he suddenly came upon a loaded hay wagon on a rolling road where there was no vision ahead; without slowing, he sliced to the left and into the overhanging hay. The fact that they emerged unscathed except for the abuse of the outraged farmer was considered by his companion to be evidence of the grace of God and of a strong belief (by Knox) in predestination.

Knox was a man of strict accounting principles. After retirement, he continued as consultant without pay to the Bureau of Child Hygiene and sometimes traveled on official business. He used his own car and paid his own living expenses on these trips but waged a long and eventually successful campaign to have the state budget officer reimburse him for gasoline—which was not authorized for private cars.

Paul Harper.

Comments on Current Literature

EPIDEMIC KERATOCONJUNCTIVITIS AND THE APC VIRUSES

AMONG the strains of virus recently recognized, and in the process of classification at the present time are the so-called "respiratory viruses." The various clinical disease manifestations have been well known for some time, and have seemed individually distinct: "flu-like colds," acute respiratory disease, or ARD, "virus pneumonia," pharyngeal-conjunctival fever, keratoconjunctivitis, et cetera. Although clues as to the nature of these strains have been accumulating for more than a decade, recent tissue culture isolation and identification have been the means of clarifying their relationships.

Epidemic keratoconjunctivitis ("shipyard eye"), prevalent in industrial areas during World War II, especially among shipyard workers, was the cause of considerable concern, not only because of the serious loss of personnel efficiency at a critical national period, but also because of the severity of the disease, which in some instances resulted in residual corneal opacities.[1, 2] Clinically the disease was characterized by acute follicular conjunctivitis, small petechial hemorrhages, enlargement and tenderness of regional lymph nodes, pseudomembrane formation, and a scanty exudate from which no significant bacteria could be cultured. In many of the cases, severe conjunctivitis was followed in about eight to ten days by keratitis. Occasionally keratitis occurred without preceding conjunctivitis. A few of the patients experienced systemic manifestations in addition to those associated with the eyes: malaise, fever, headache, generalized aching. In 1943 Sanders and Alexander[2] isolated an infectious agent, viral in nature, from the eye washings from a patient whose clinical manifestations were considered typical. The virus seemed to be established readily in serial mouse-brain passage, and mild symptoms could be produced in human volunteers by this mouse-adapted agent. Apparently the strain was not maintained, however, and some confusion arose as to its identity. Since that time the disease has occurred periodically in epidemic form, and a viral agent has been isolated in a number of instances from the eye washings of patients with epidemic keratoconjunctivitis. The virus was grown successfully in embryonated eggs by graft of human corneal cells to the chorioallantoic membrane,[3] and was established in mice, with signs of infection similar to those described in mice by Sanders and Alexander.

The APC group of viruses (adenoidal-pharyngeal-conjunctival) was discovered by Rowe and Huebner and their associates,[4] the original investigation being stimulated by the recovery of a cytopathogenic agent from adenoid tissue undergoing spontaneous degeneration in tissue culture. About this time an agent apparently very similar was isolated by Hilleman and Werner[5] from patients with acute respiratory disease (RI 67 virus). These two agents cultivated in tissue culture gave presumptive evidence of immunologic relationship. Subsequently the APC viruses were shown to comprise a potentially large

group of agents which could be subdivided into types by means of type-specific neutralization tests.[4]

Thus within a relatively brief period of time the APC viruses are being classified immunologically and established as the causative agent in several clinical entities[6]: acute respiratory disease such as that prevalent in recent years among military personnel and recruits (ARD) classified as Type 4 APC, and believed to be identical with the RI 67 strain; epidemic outbreaks of "pharyngoconjunctival fever" associated with Type 3 APC virus; "simple conjunctivitis," and the so-called "swimming bath conjunctivitis" associated with Types 3 and 4. Types 3, 4, and 7 have been recovered from patients among military recruits suffering from respiratory illness ranging in severity from a mild upper respiratory infection to virus pneumonitis. Types 1, 2, 3, and 5 were isolated from patients suffering from a relatively mild pharyngitis, and have been obtained from surgical specimens of adenoid and tonsillar tissue.

The causal relation of the APC viruses to epidemic keratoconjunctivitis ("shipyard eye") is a matter of recent investigation. Concerning this relationship informative discussions took place at the June, 1955, meeting of the Association for Research in Ophthalmology (Proceedings recorded in the *American Journal of Ophthalmology* for November, 1955). Several of the papers presented and discussed there, and one appearing subsequently, are of special interest in this connection. Fowle, Cockeram, and Ormsby[7] of the University of Toronto reported three isolations of virus from patients with keratoconjunctivitis, each with slightly different clinical manifestations of the disease. One of the three patients had suffered from pharyngitis about five days prior to the onset of a severe follicular conjunctivitis. All three developed keratitis with resulting corneal opacities. The viral agents were isolated in tissue culture by inoculation of monkey kidney epithelial cell or HeLa cell preparations with tears or eye washings from infected eyes. Their cytopathogenic effect in these tissues was distinctive and progressive. The agents could be propagated also in human corneal epithelial cells, in human kidney epithelial cells, and could be adapted to the chorioallantoic membrane of the hen's egg by the use of human corneal tissue grafts. Rabbit cornea in vivo and rabbit corneal-epithelium growing in tissue culture were not susceptible to infection with these strains. A transient illness occurred in mice following inoculation, but the agents could not be established in mice. Mild characteristic disease was produced in a human volunteer, and the viral agent was recovered again from him by tissue culture of eye washings. Significant increases in neutralizing antibody could be demonstrated in serum specimens of both the patients and the volunteer, and all three strains of virus were identified immunologically as belonging to Type 3, APC group.

At the same meeting of the Association for Research in Ophthalmology, Jawetz and his co-workers[8] (San Francisco) presented the results of a rather extensive investigation of epidemic conjunctivitis and keratoconjunctivitis, and reported the isolation from a patient showing typical clinical manifestations of epidemic keratoconjunctivitis of a viral agent identified serologically, both by neutralization and by complement fixation, as belonging to the APC viruses, Type 8. This strain of virus, which was called "Trim" from the name of the patient, was neutralized by specific Type 8 immune serum, and by pooled human gamma globulin, but was not neutralized by any antiserum of Types 1, 2, 3, 4, 5, 6, or 7 APC viruses. Likewise, specific immune serum (rabbit), developed to "Trim" virus experimentally, failed to neutralize the APC virus of Type 3 which has been recovered previously from patients with epidemic keratoconjunctivitis. In this study of epidemic

keratoconjunctivitis by Jawetz and his associates twenty-five other patients with typical keratoconjunctivitis, unidentified etiologically by specific isolation of virus, showed significant concentrations of neutralizing antibodies to the Type 8 strain.

With respect to the patient, Trim, an interesting situation developed. The nurse who attended him developed keratoconjunctivitis within ten days following this exposure; eye washings taken on the sixth day of her illness yielded no virus, but on the fourteenth day of her illness a viral agent was recovered which was readily identified as herpes simplex. During the illness she developed an increasing titer of type-specific antibody to APC virus, Type 8. This same observation was made concerning another patient in the series whose keratoconjunctivitis was due apparently to herpes simplex virus. The authors raise the question of possible dual infection in some cases of keratoconjunctivitis. They make the interesting suggestion that since the APC viruses can occur in cases of conjunctivitis without keratitis, perhaps infection with APC virus may activate a latent herpes simplex, and that such might have been the situation in some of the more severe cases of epidemic keratoconjunctivitis in which residual corneal opacities were a serious problem. As the authors state, this hypothesis seems worthy of consideration for future study even in the absence of supporting evidence at present.

In a more recent issue of the *American Journal of Ophthalmology*[9] (February, 1956) the same group of investigators reports the isolation of Type 6 APC virus from two patients with follicular conjunctivitis associated with systemic and respiratory symptoms. Both patients developed increasing titer of antibody to Type 6 virus during the course of clinical illness. This report represents the first definite evidence of clinical illness due to Type 6 APC virus, the sequence of clinical signs and symptoms suggesting the eye as the portal of entry. This strain (Type 6) was one of those encountered in adenoid tissue undergoing spontaneous degeneration in tissue culture[4]; it is known to occur in human populations from surveys of neutralizing antibodies to APC viruses, about 30 per cent of a fair random sample of the general population in the Washington, D. C., area being positive.[4] In connection with the isolation of Type 6, Jawetz and his associates conducted a survey of persons, aged 9 to 44 years, living in California. Thirty-three per cent of the serum specimens obtained between 1952 and 1955 showed appreciable titers of neutralizing antibodies to Type 6 APC virus. The majority of these positive serum specimens was obtained from persons over the age of 25 years. These authors consider the eye an important portal of entry for APC virus infection. "In spite of the frequent association of APC virus infection with respiratory disease, it appears possible that the conjunctiva frequently serves as a portal of entry for APC viruses. Conjunctivitis may occur alone, or may precede the onset of pharyngitis or systemic symptoms."[9] Thus it seems probable that more than one type of APC virus may be involved in the epidemiology of epidemic keratoconjunctivitis.

Because of their prevalence among military personnel and recruits, the APC viruses are currently under intensive investigation, particularly from the standpoint of vaccine preparation and its efficacy, and studies of APC infections are being carried out wherever epidemics occur as well as in human volunteers.[10] Reports of the work of Bell, Hantover, Huebner, Loosli, and their associates[11] appear in recent issues of the *Journal of the American Medical Association* (August 18, 1956) and the *American Journal of Public Health* (September, 1956). A trivalent vaccine, formaldehyde-inactivated APC virus of Types 3, 4, and 7, has been employed in preliminary studies with apparent success, the progress reports indicating substantial

reduction in the expected occurrence of these infections. Likewise, investigations as to the nature of the various strains of virus are in progress in a number of laboratories. Recently the general group name, adenoviruses, has been proposed.[11] From the theoretical viewpoint it is of considerable interest whether these types of APC virus represent distinct strain entities, or can be explained on the basis of possible virus mutation activity, and from the practical point of view, the development of an effective vaccine may offer the clinician an opportunity for the control of these troublesome infections.

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News and Notes

The annual meeting of the **American Academy of Pediatrics** was held in New York on October 10. Dr. Stewart H. Clifford was elected Vice-President and President-Elect. Dr. Edgar E. Martmer, President-Elect, took over the presidency for 1956-1957.

The Council of Biological and Medical Abstracts, Ltd., composed of representatives from the various British associations and societies of the biological sciences, announces the change in the name of British Abstracts of Medical Sciences to the **International Abstracts of Biological Sciences.** In addition to abstracts of the world literature in the various biological fields, beginning in 1957 the journal will include translations of important Russian papers simultaneously with their Russian publication, through an arrangement with the Academy of Sciences of the U.S.S.R.

Baylor University College of Medicine, Southwestern Poliomyelitis Respiratory Center, and the **Jefferson Davis Hospital,** in cooperation with the **National Foundation for Infantile Paralysis, Inc.,** announce their fourth postgraduate course for physicians, nurses, medical social service workers, and physical and occupational therapists, to be held February 25 through March 1, 1957. The course on "Practical Management of Poliomyelitis and Principles of Rehabilitation" will cover complete care of poliomyelitis with emphasis on the severely involved patient, the effective coordination of services and the principles of rehabilitation. For further details write to Dr. William A. Spencer, Medical Director, Southwestern Poliomyelitis Respiratory Center, Education Office, 1300 Kenwood Lane, Houston, Texas.

The **Sister Elizabeth Kenny Foundation** announces a program of postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of neuromuscular diseases. The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5,000 to $7,000 a year, depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada will be eligible. Inquiries regarding details of the program should be addressed to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2, Minn.

A Postgraduate Course in Tuberculosis and Other Pulmonary Diseases in Childhood will be offered by the staff of the Children's Chest Service at **New York University-Bellevue Medical Center** from April 22 through April 26, 1957. Sessions will be devoted to the pathogenesis, course, diagnosis, and treatment of tuberculosis and other chest disorders in infants, children, and adolescents, with demonstrations on bronchography, tomography, and pertinent new developments in microbiology. For further information write to the office of the Dean, Post-Graduate Medical School, 550 First Ave., New York 16, N. Y.

Books

Diseases of the Chest. H. Corwin Hinshaw and L. Henry Garland, Philadelphia, 1956, W. B. Saunders Co.

This volume was prepared by an internist who has had many years of critical experience in clinical practice, teaching, and research and by a radiologist of like background. The result is an excellent, practical, and sound volume which will serve both the student and the practitioner.

The first four chapters are devoted to diagnostic procedure. Then follows a clear description of the anatomy of the pulmonary system and a chapter by Dr. Roger Wilson on pulmonary function. The subsequent five chapters deal with inflammatory diseases and their sequelae. About 180 pages deal with tuberculosis. Dr. William Winn wrote the chapter on coccidioidomycosis. The chapters on foreign bodies by Dr. Walter Heck and those on asthma, emphysema, and congenital anomalies will also be of special interest to the pediatricians.

There are many excellent illustrations, mostly radiologic. The references are well chosen and recent. They include especially review articles which will in turn guide the reader to other important references.

The book is interesting, readable, and informative. The pediatrician might wish for more complete descriptions of such conditions as hyaline disease of the lung, atelectasis of the newborn, cystic fibrosis of the pancreas, and for deletion of such terms as "mucoviscidosis." However, the coverage of other conditions which internists see more frequently but which nevertheless occur also in the pediatric age group is so good and so thorough that all interested in children will find this book a most welcome addition.

Masked Epilepsy. Hugh R. E. Wallis, M.D., M.R.C.P., Baltimore, 1956, Williams & Wilkins Co., 51 pages. Price $2.50.

In this short monograph the author, a pediatrician of Bath, England, presents under the title *Masked Epilepsy* his theory that many nonconvulsive conditions in childhood are due to epilepsy. In addition to the types of case usually described as "visceral epilepsy," where the periodic attacks are considered by some to be "equivalents," the author theorizes that "masked epilepsy" may be the cause of many other conditions. Among these he includes recurrent headache, cyclic vomiting, night terrors, somnambulism, temper tantrums, three-month colic, hypoglycemia, failure to gain weight, and sudden cardiac arrest. The evidence presented in the monograph is quite inadequate to support his theory. Probably the reason for the presentation of his theory in monograph form lies in the ideas and theory being so unsupported by evidence or proof that it would not be acceptable for publication in most medical journals.

Directory for Exceptional Children. Edited by E. N. Hayes, Boston, 1956, Porter Sargent Publisher, 256 pages. Price $4.00.

A useful book of reference containing lists by states of schools for exceptional children according to the particular trouble or handicap. Directories for schools for the mentally retarded, tutoring and remedial schools, emotionally disturbed and maladjusted, blind, deaf, speech handicapped, and for children with orthopedic conditions and cerebral palsy are included.

Diseases in Infancy and Childhood, ed. 2. Richard W. B. Ellis, M.D., F.R.C.P., Baltimore, 1956, Williams & Wilkins Co., 710 pages.

This textbook by the professor of child life and health at the University of Edinburgh has been fully revised. It is a well-written text for the student and practitioner, rather than an exhaustive reference text. The illustrations, which number over 300, are unusually good and well selected. The author has gathered congenital anomalies into one section rather than bringing them in by systems.

Editor's Column

THE PROLONGATION OF FATAL ILLNESSES

SOONER or later a problem that haunts the mind of the conscientious practitioner is the question of prolongation of life in what is recognized as a fatal illness. Is the physician justified in using every recognized agent, as well as those whose value is uncertain? It is a moral or ethical question without a simple or easy answer. Over the years we have heard it discussed many times in many situations, and of necessity the conclusions merely reflected personal opinion. Many factors enter into the problem when a specific patient is under discussion.

In this issue we present a discussion of one of the aspects of the question involving a specific disease, leukemia. In some ways it is an unusual discussion to appear in a medical journal, but we feel the findings of the study are of importance to physicians who are having to face the problem in this specific disease with increasing frequency. From a scientific viewpoint, the use of the drugs now being employed to bring about remissions is fully justified, as it is only in this way we can hope to find a cure.

On the other hand, there is always a very human problem involved. The findings of the study by Dr. Cobb (page 746), at the M. D. Anderson Hospital in Texas, of the reactions of the family circle to the prolongation of life of children with leukemia will be of great moral help to the physician who has to make the decision.

HYPERTHERMIA

TEMPERATURE recordings above 41° C. (105.8° F.) are uncommon. E. F. Dubois in "Fever and the Regulation of Body Temperature" states that temperatures of this height may be harmful, and that a temperature of 42° C. (107.6° F.) may be dangerous to life if prolonged for even a few hours. There are a number of authentic cases reported where the temperature reached as high as 44° C. (111.2° F.). These were associated with fatal cases of brain trauma, convulsive seizures, and meningitis. Temperatures of this height have also been reported as being observed in sunstroke, and a few of these patients are said to have recovered.

Judging from medical literature there has been little interest in hyperthermia in recent years, but the literature of the period 1880 to 1895 contains many case reports. In these, temperatures of 113° to 117° F. (45° to 47° C.) are not infrequently reported, and a few are reports of cases

where such fantastic figures as 148°, 151°, and 157° F. (65° to 70° C.) were considered as authentic. Ch. Richet, of Paris, published a book on the subject in 1899, *La Chaleur Animale*, and Volume I, 1894, of *Guy's Hospital Reports* contains a paper by Dr. J. H. Bryant on "One Hundred Cases of Hyperthermia," in which he collected cases from the literature and added a few of his own. Let it be added that he was suspicious of some. Many of the reported cases with hyperthermia were in patients with "hysteria," and the conclusion is inevitable that the high temperatures in many instances were due to fraud.

The cases with the fantastic temperatures make rather hilarious reading. The amazing thing is how some physicians of high reputation and standing were hoodwinked and their judgment warped. One of these was Dr. Abraham Jacobi, who reported a case as authentic before the meeting of the Association of American Physicians in 1895, in which the temperature reached 148° F. (64.4° C.). The case report is published in great detail in Volume X, 1895, of the Transactions of that society, and is unique in that the patient was a "thoroughly hysterical" *male*. In addition to many pages of bedside notes, the author lists two and one-half pages of the hysterical manifestations observed during the patient's stay in hospital.

Obviously some of the members sensed fraud. Dr. Wm. H. Welch, in discussing the paper, remarked, "Dr. Jacobi must pardon me if, with the greatest respect for his skill as an observer, I express complete scepticism as to the trustworthiness of these observations. I do not undertake to explain in what way the deception was practiced, but there is no doubt in my mind that there was deception. Such temperatures . . . are far above the temperature of heat-rigor of mammalian muscle, and are destructive of the life of animal cells."

Dr. Jacobi stuck by his guns, to judge from his remarks closing the discussion. "Dr. Welch is welcome to his scepticism . . . in these last few days . . . the temperature ranged from 109.8° to 148°, with an average of 124° or 125°. Now these are the facts. If our physiology and if our theory does not agree with these facts, well, so much the worse for the undeveloped state of our physiology and our theory." Dr. George Dock asked if the temperature of the urine had been taken, and the answer was this had been neglected. Dr. Osler contributed but one short question. "Was his abdomen very hot?" The reply: "Sometimes very hot and sometimes not so."

The case in which the temperature was said to have reached 157° F. (70° C.) was reported by Dr. Heber Jones in the *Memphis Medical Journal* of October, 1891. Dr. Jacobi, in referring to this case, accepted its authenticity and remarked "that Dr. Heber Jones' standing as a medical man and as a gentleman is of the very highest in his community" (as was Dr. Jacobi's) "and that a dozen physicians and nurses were observers of the facts narrated." So far as we can learn, the means of the deception were never ascertained.

The case report by Dr. W. J. Galbraith in the *J.A.M.A.*, March 31, 1891, in which the third fantastic temperature (151° F.) was reported is of even more interest, as it was

shown to be fraudulent and the patient was caught in other types of malingering. In the September issue of the *Omaha Clinic* Dr. J. C. Sommers, who had operated upon the patient, published a report with the title "Omaha's Remarkable Case of High Temperature—an Undoubted Hysterical Fake." Still later, in the February, 1892, issue of the same journal, Dr. C. T. Poe published a report entitled "A Chronic Malingerer." It seems Dr. Poe had the patient under observation some two years before Dr. Galbraith. During this time she had attempted to palm off a temperature of 112° F., which it was discovered was produced by heating the thermometer with a hot-water bottle in the bed.

We recall the discomfiture of one of our colleagues a number of years ago who was treating a student nurse for complaints suggestive of a renal condition. Her temperature suddenly went to 108° F. (42.2° C.). An emergency section disclosed nothing abnormal. It was later disclosed that the hyperthermia resulted from pressure of the thermometer against an electric light bulb.

We know of no cases where "hyperthermia" due to malingering has been reported in children. Hyperthermia at this age period is usually an indication of a severe infection and of bad prognosis. The highest temperature we have ever seen was 108° F. (42.2° C.) in a boy with meningitis shortly before death.

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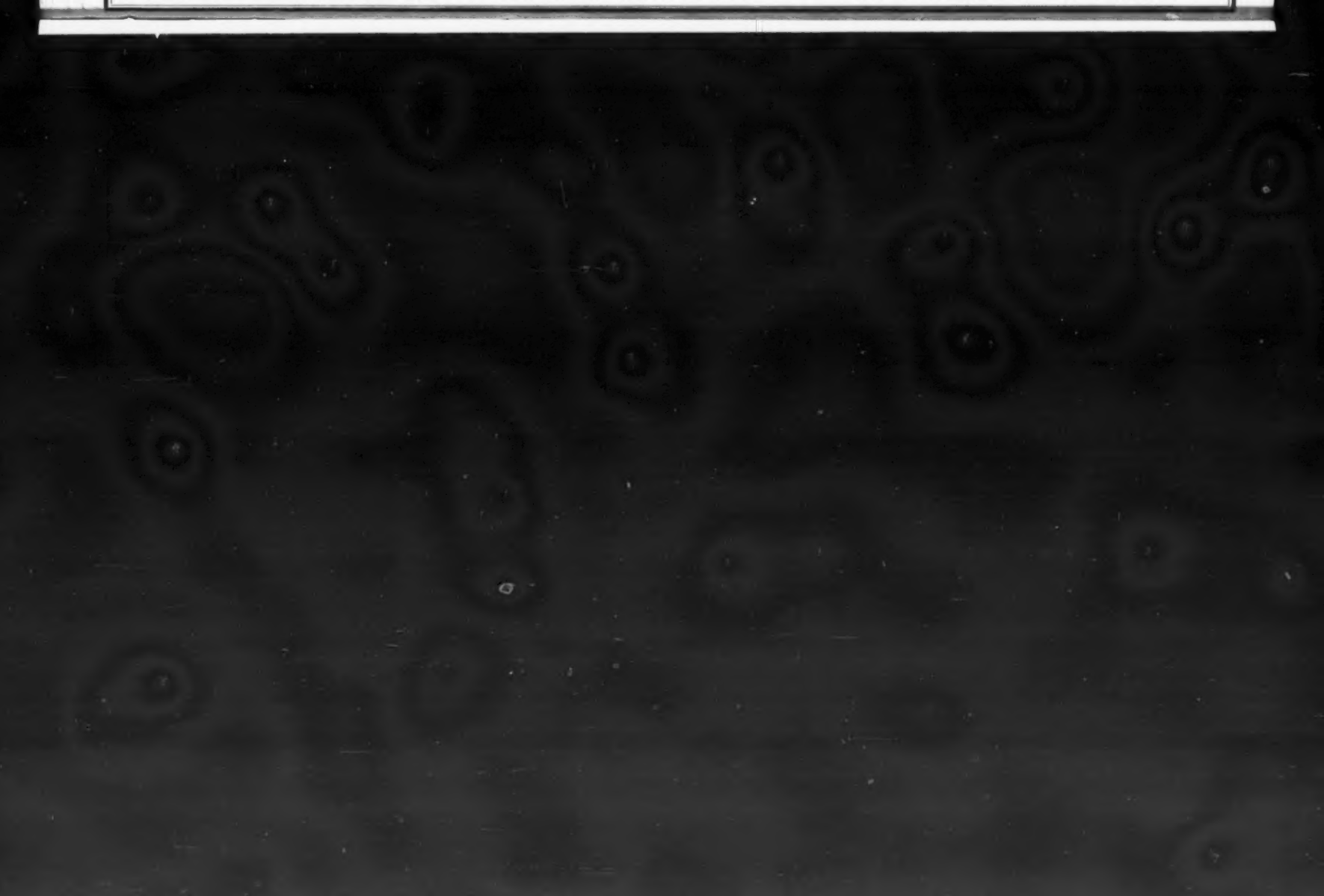

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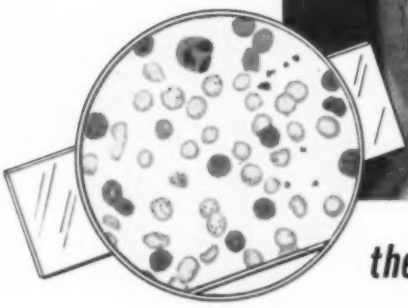
Each 4-ml. teaspoonful of light green, lemon-lime flavored Serpasil Elixir contains 0.2 mg. of Serpasil.

CIBA
Summit, N. J.

Heavy Metal Poisoning



the incidence is higher than realized

Calcium Disodium **VERSENATE***

spells the answer

At last, here is a dependably effective means of removing heavy metals from the body *without danger of organ damage.* Calcium Disodium VERSENATE is now available for oral as well as intravenous therapy; the intravenous form for safe, effective, dramatic short-term treatment; the oral form for convenient prevention of exacerbations or as sole therapy for milder types of lead poisoning.

NOW IN 2 DOSAGE FORMS

Write for descriptive booklet

INTRAVENOUS Complete instructions for dilution and administration accompany the ampuls. The average daily dose for children is not more than 0.5 Gm. per 35 pounds of body weight, given once or twice daily. (Adult dose, 1 to 2 Gm. per day, given as two infusions.) In boxes of six 5 cc. (1 Gm.) ampuls.

ORAL For children, the dose is adjusted on the basis of 2 tablets (1 Gm.) per 35 pounds of body weight daily, in divided doses. For ease of administration tablets may be crushed and dissolved in milk. (Average adult dose is 8 tablets (4 Gm.) per day, in divided doses.) In bottles of 250 tablets, each containing 500 mg.

*Trademark of Dow Chemical Co.

Riker LOS ANGELES

FURACIN®

BRAND OF NITROFURAZONE

The most widely-used topical antibacterial—
in formulations especially effective
for infections of the eye, ear and nose

ophthalmic

"... Furacin is an effective antibacterial drug which may be safely prescribed for a variety of conditions involving the external eye and lids."[1]

Rapid, effective antibacterial action with unique lack of irritation. Indicated in external ophthalmic bacterial infections including conjunctivitis, blepharitis, dacryocystitis, keratitis, hordeolum, lid abscesses and for the prevention of postoperative infections.

FURACIN Ophthalmic Liquid: 15 cc. dropper bottle.
FURACIN Ophthalmic Ointment: 3.5 Gm. tube.

ear solution

In 120 cases of otitis treated, "the results have been excellent as compared to results obtained previously."[2]

Prompt antibacterial and deodorizing action in otitis externa and media. It is nonirritating to the infected epithelial surfaces of the external canal.

FURACIN Ear Solution: 15 cc. dropper bottle.

nasal

"Intranasal and sinus infections have been found to disappear more promptly ... helps to combat the associated nasopharyngitis. ..."[3]

Topically effective antibacterial (with vasoconstrictor) indicated in rhinitis, nasopharyngitis and sinusitis. There is no irritation or stinging, or slowing of the ciliary beat.

FURACIN Nasal with ephedrine: 15 cc. dropper bottle.
FURACIN Nasal with Neo-Synephrine*: 15 cc. dropper bottle.

*Neo-Synephrine—reg. trademark Winthrop Laboratories, Inc., brand of phenylephrine.

REFERENCES: 1. Brennan, J. W.: Am. J. Ophth. **35**:1343, 1952. 2. Anderson, J. R., and Steele, C. H.: Laryngoscope **58**:1279, 1948. 3. Spencer, J. T., in Conn, H. F.: Current Therapy 1954, Philadelphia, W. B. Saunders Co., 1954, p. 130.

EATON LABORATORIES NORWICH, NEW YORK

NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides

nonirritating, hypoallergenic shampoo

PROOF

does not irritate the skin

Johnson's Baby Shampoo produces no evidence of irritation even after full-strength patch tests for 10 consecutive contact periods of 24 hours each.

and does not irritate the eyes

No evidence of irritation—even when introduced into conjunctival sacs of rabbits t.i.d. for as long as 15 days.

- contains no soap, no harsh detergents
- cleanses thoroughly—rinses completely
- helps combat scaling, crusting, cradle cap

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

NEW PRODUCT

"CLUSIVOL"® syrup

Multiple vitamins-minerals

in a candy-flavored base

The candy taste of "Clusivol" Syrup appeals particularly to children but is also enjoyed by older individuals who prefer a liquid preparation.

To facilitate administration, a dripless, unbreakable plastic dispenser is supplied free with the 8 ounce bottle.

10 cc. (2 teaspoonfuls) contains:

Vitamin A	5,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units
Vitamin C	40.0 mg.
Vitamin B_{12}	4.0 mcg.
Thiamine HCl (B_1)	2.0 mg.
Riboflavin (B_2)	2.0 mg.
Nicotinamide	10.0 mg.
d-Panthenol	6.0 mg.
Pyridoxine HCl (B_6)	1.2 mg.
l-Lysine HCl	25.0 mg.
Cysteine HCl	5.0 mg.
Inositol	5.0 mg.
Choline*	5.0 mg.
Iron*	3.0 mg.
Calcium*	40.0 mg.
Phosphorus*	30.0 mg.
Iodine*	75.0 mcg.
Potassium*	2.5 mg.
Manganese*	0.5 mg.
Zinc*	0.5 mg.
Magnesium*	3.0 mg.

*Supplied as choline bitartrate, ferrous gluconate, calcium lactate and the hypophosphite, calcium hypophosphite, potassium iodide, potassium gluconate, manganous gluconate, zinc glycerophosphate and magnesium gluconate.

DOSAGE: *Children* — 1 to 2 teaspoonfuls (5-10 cc.) daily.
Adults — 2 teaspoonfuls (10 cc.) twice daily, or as required.

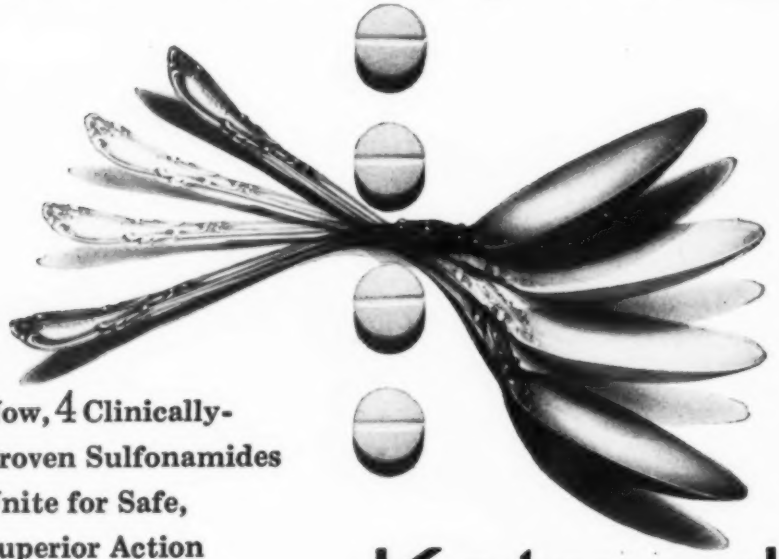
SUPPLIED: "Clusivol" Syrup — No. 948 is presented in 8 oz. (with dispenser) and 16 oz. bottles.

Also available: "Clusivol" Capsules — No. 293 — Bottles of 100 and 1,000.

Ayerst

5684 AYERST LABORATORIES • New York, N. Y. • Montreal, Canada

Pluralizes Potency 4 Times!



Now, 4 Clinically-Proven Sulfonamides Unite for Safe, Superior Action

Katrasul

Chimedic

By combining 4 powerful sulfas in one palatable preparation, Katrasul provides a broad-spectrum of activity 4 times as potent as any single sulfa—with toxicity reduced to practically zero.

Katrasul's quadruple formula includes Sulfadiazine, Sulfamerazine, Sulfamethazine and Sulfacetamide—individually notable for antibacterial action—in combination exerting a 4-way antibacterial spectrum of unmatched efficacy and power.

Using only fractional dosage of each sulfa results in greater solubility and the virtual elimination of crystalluria. Sensitization reactions and toxic effects approach zero.

Prescribe Katrasul to combat both gram positive and gram negative bacilli. It is effective not only against the common micro-organisms, but also the gonococcus, meningococcus, pneumococcus, staphylococcus and streptococcus infections.

Delightful coconut-custard flavor invites patient- acceptance.

•

Prompt action, safety, and pleasant taste make Katrasul highly useful in the treatment of children's infectious diseases.

•

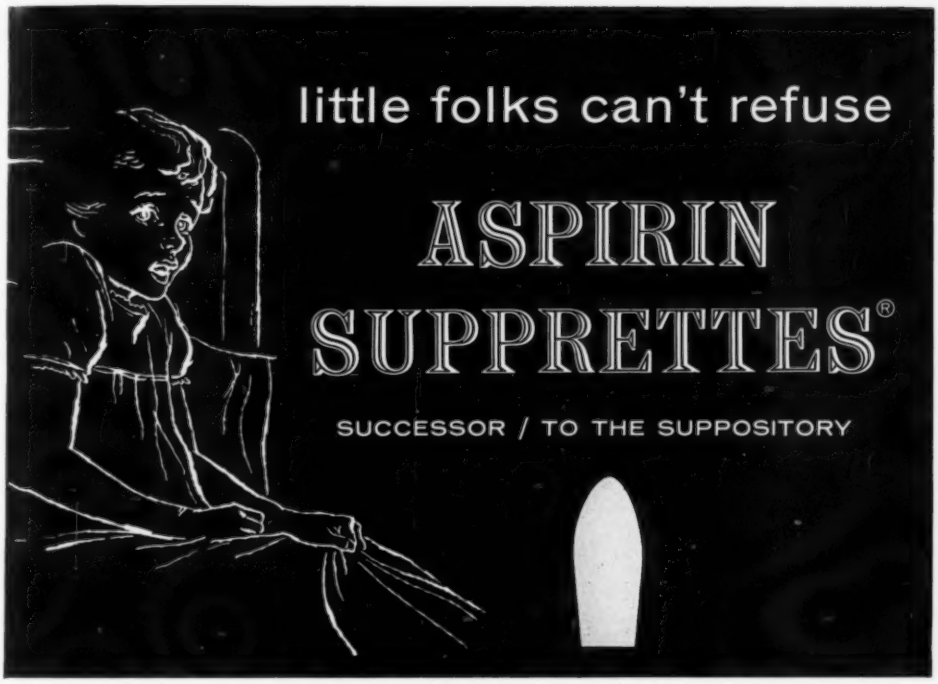
Available: Delicious coconut-custard flavored suspension. 4oz., pints, gallons. Also in tablets.

CHICAGO PHARMACAL COMPANY

5547 N. Ravenswood Ave., Chicago 40, Illinois

Pacific Coast Branch

381 Eleventh St., San Francisco, Calif.



Now you can be sure your patients receive full therapeutic doses of salicylates. Aspirin Supprettes rectally achieve the same salicylate blood levels as do equal oral doses, without gastric or rectal irritation.

ASPIRIN SUPPRETTES

- Ideal when oral therapy is difficult or impossible
- In febrile conditions accompanied by nausea or vomiting
- To eliminate local gastric irritation
- For prolonged salicylate therapy
- In rheumatic fever
- For relief of emotional trauma of fever, pain, insomnia

ASPIRIN w/SECOBARBITAL SODIUM SUPPRETTES

- For safe, rapid sedation of short duration
- In insomnia, anxiety states
- To quiet hyperexcitability
- Preoperatively

SUPPLIED:

Aspirin Supprettes: 1 gr., 3 gr., 5 gr. and 10 gr.
Aspirin w/Secobarbital Supprettes:
No. 1—(aspirin 1 gr., secobarbital sodium ⅛ gr.).
No. 2—(aspirin 3 gr., secobarbital sodium ⅜ gr.).
No. 3—(aspirin 5 gr., secobarbital sodium ⅝ gr.).
No. 4—(aspirin 10 gr., secobarbital sodium 1¼ gr.).
IN JARS OF 12.

THE "NEOCERA" BASE MAKES THE DIFFERENCE

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent.
*Trademark U.C.C.

ASPIRIN SUPPRETTES and ASPIRIN w/SECOBARBITAL SODIUM SUPPRETTES

NO REFRIGERATION NECESSARY

Samples on Request

Webster

THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENN.

"Functional vomiting

should be carefully distinguished from organic vomiting. Grave consequences may follow if evidences of organic derangement . . . are masked by treatment designed to control vomiting alone."[1]

SAFE

Safety First | in emesis therapy

Prescribe

EMETROL®

(Phosphorated Carbohydrate Solution) *First*

SAFE

EMETROL will not suppress symptoms arising from organic etiology. It controls vomiting of functional origin quickly.

Dosage: Adults, 1 or 2 tablespoonfuls; infants and children, 1 or 2 teaspoonfuls, as often as every 15 minutes. Always administer *undiluted,* and forbid oral fluids for at least 15 minutes after each dose. Even if first dose is not retained, continue administration. If vomiting is not controlled within one or two hours, look for organic etiology. For individual dosage regimens in various indications, please send for literature.

1. Bradley, J. E.: Mod. Med. 20:71, No. 20, 1952.

SAFE

Kinney **KINNEY & COMPANY, INC.** Columbus, Indiana

FOR MORE

DEPENDABLE

SULFONAMIDE

THERAPY

ALDIAZOL-M®

Aldiazol-M combines two of the most effective sulfonamides, sulfadiazine and sulfamerazine, with a systemic alkalizer, sodium citrate. High, prolonged blood levels are assured, while the danger of crystalluria is reduced.

Because of its inherent safety, it is often prudent to use Aldiazol-M instead of antibiotics and thus preclude the risk of sensitization.

Supplied as a suspension and as a tablet

Each teaspoonful contains:

Sulfadiazine*	0.25 Gm.
Sulfamerazine*	0.25 Gm.
Sodium Citrate	1.00 Gm.

Each tablet contains:

Sulfadiazine*	0.125 Gm.
Sulfamerazine*	0.125 Gm.
Sodium Citrate	0.250 Gm.

*Microcrystalline

The S. E. Massengill Company

Bristol, Tennessee

New York • Kansas City • San Francisco

New Physiologic Aid in Constipation

DOXINATE®

(Dioctyl Sodium Sulfosuccinate, Lloyd)

THE ORIGINAL FECAL SOFTENER

"...we have been impressed..."*

"Impressive" is, indeed, the word for the entirely new fecal softening action of Doxinate. Doxinate eliminates the primary complication of constipation—hard, dry stools—and eases evacuation by restoring soft, normally formed feces. It is neither laxative, lubricant nor bulk producer.

Two new studies on the action of dioctyl sodium sulfosuccinate found it an effective, safe and easily administered aid to normal colonic function. Antos** called his results with the medication "uniformly good" and Spiesman and Malow* considered it "a very considerable advance in the prevention and treatment of constipation."

Optimum fecal softening is obtained with 2 or 3 capsules (120-180 mg.) a day. Easy passage and improved frequency of movement provide real patient satisfaction. Your patients, too, will benefit from restoration of normal bowel habits with Doxinate, the new physiologic aid in constipation.

DOSAGE:

ADULTS: 2 or 3 capsules daily.
INFANTS: 1 or 2 cc. once daily in milk, formula or fruit juice.

SUPPLIED:

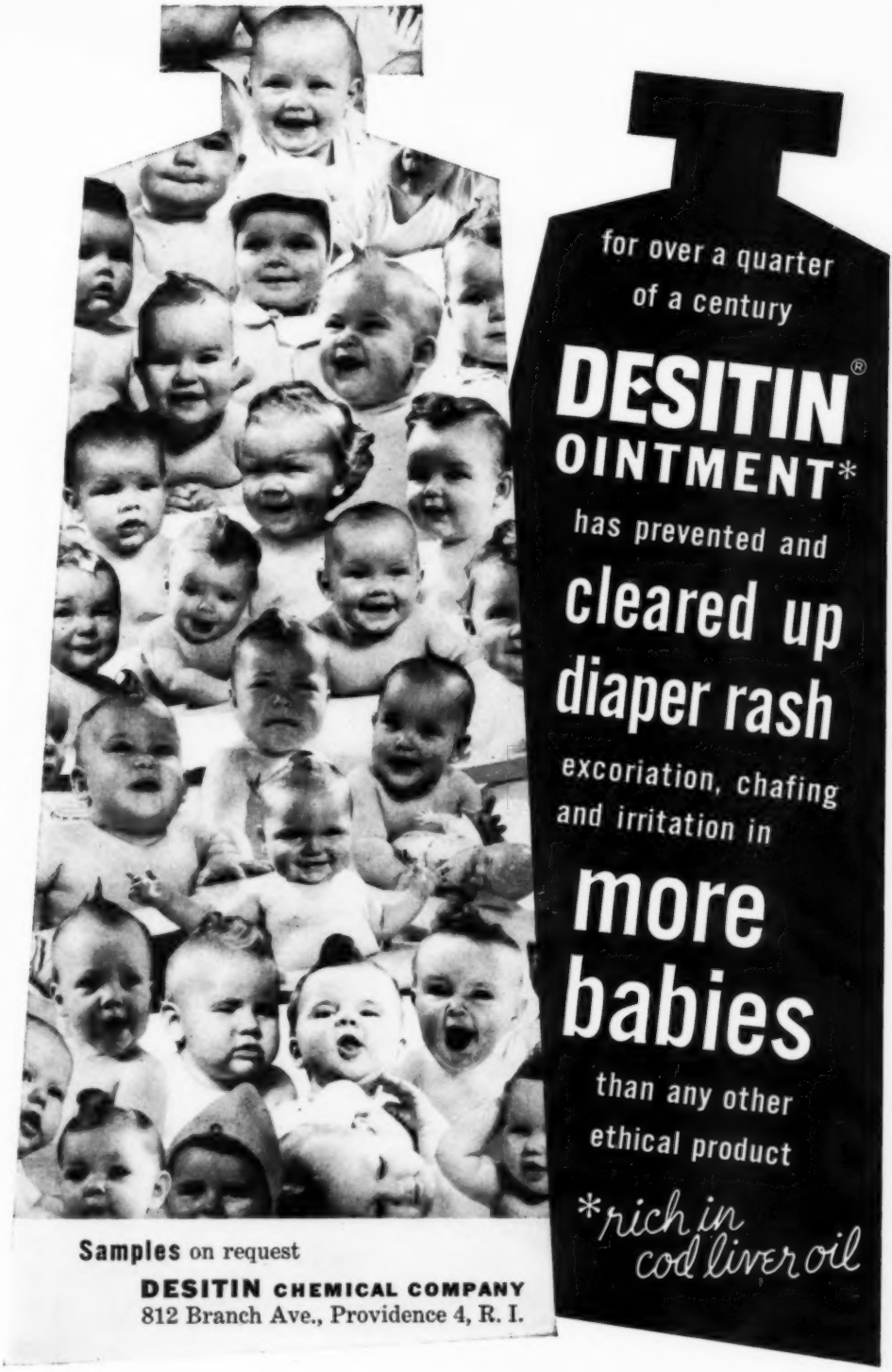
DOXINATE CAPSULES: each green transparent capsule contains 60 mg. dioctyl sodium sulfosuccinate—bottles of 30 and 100.

†DOXINATE SOLUTION 5%: each 1 cc. contains 50 mg. dioctyl sodium sulfosuccinate; 60 cc. bottle with dropper calibrated at 1 cc.
†New standard dosage form.

LLOYD
BROTHERS, INC.
Cincinnati 3, Ohio

*Spiesman, M. G., and Malow, L.: New Fecal Softener (Doxinate) in the Treatment of Constipation, Journal-Lancet 76:164 (June) 1956.

**Antos, R. J.: A New Approach to the Treatment of Severe Constipation, Southwestern Med. 37:236 (April) 1956.



Samples on request

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

Upjohn

Delta-Cortef* for inflammation, neomycin for infection:

Neo-Delta-Cortef†

TOPICAL OINTMENT

Each gram contains:

Delta-1-hydrocortisone acetate 5 mg. (0.5%)

Neomycin sulfate . . . . . 5 mg.
(equiv. to 3.5 mg. neomycin base)

Methylparaben . . . . . 0.2 mg.

Butyl-p-hydroxybenzoate 1.8 mg.

Supplied: 5-gram tubes

EYE-EAR OINTMENT

Each gram contains:

Delta-1-hydrocortisone acetate 2.5 mg. (0.25%)

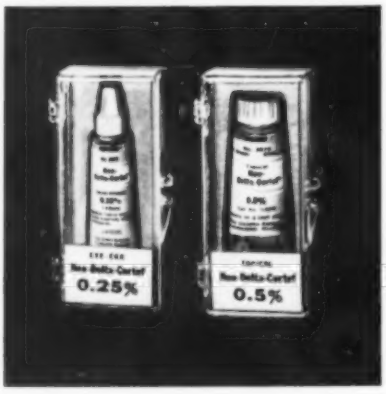
Neomycin sulfate . . . . . 5 mg.
(equiv. to 3.5 mg. neomycin base)

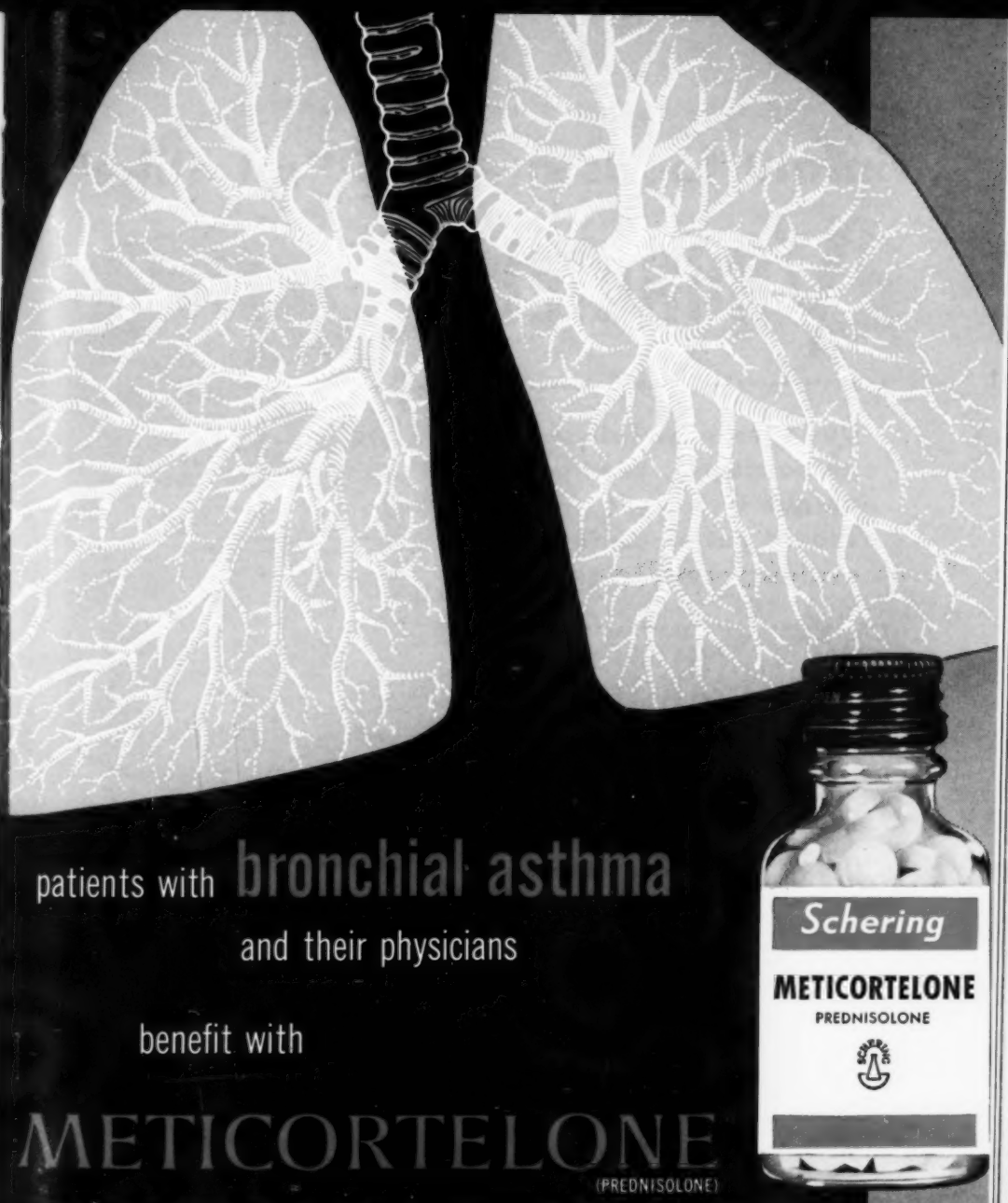
Supplied: ⅛ oz. tubes with applicator tip

*TRADEMARK

†TRADEMARK FOR THE UPJOHN BRAND OF PREDNISOLONE ACETATE WITH NEOMYCIN SULFATE

The Upjohn Company, Kalamazoo, Michigan





patients with **bronchial asthma**

and their physicians

benefit with

METICORTELONE

(PREDNISOLONE)

for patient

rapid relief of bronchospasm, dyspnea; permits effective cough following bronchodilating action; vital capacity and pulmonary function improved...electrolyte imbalance unlikely...hastens rehabilitation

for physician

facilitates inhalational and other adjunctive therapy; far smaller dosage than with oral hydrocortisone ...little or no worry about edema, sodium retention, potassium loss... patient cooperation assured

buff-colored tablets of 1, 2.5 and 5 mg.

METICORTELONE,® brand of prednisolone.

ML-J-1976

infant foods are *not* "all alike"

VARAMEL

Designed especially for pediatric use, Varamel is unique in its field and should not be confused with ordinary evaporated milks.

FIRST—Varamel is made exclusively from Grade A Milk*, thus assuring a high quality, clean milk from the source of supply to the infant.

SECOND—Varamel is fortified with sufficient pure synthetic vitamins to provide the daily recommended allowance of all known essential vitamins.

THIRD—The butter fat is replaced by vegetable and animal fats which are particularly well-tolerated and utilized by the infant.

FOURTH—Iron is added to supply 7.5 milligrams per quart of formula.

FIFTH—Varamel contains only the sugar from the milk used, so the physician can add the necessary amount of carbohydrate to meet the nutritional needs of the infant.

Approximate Analysis

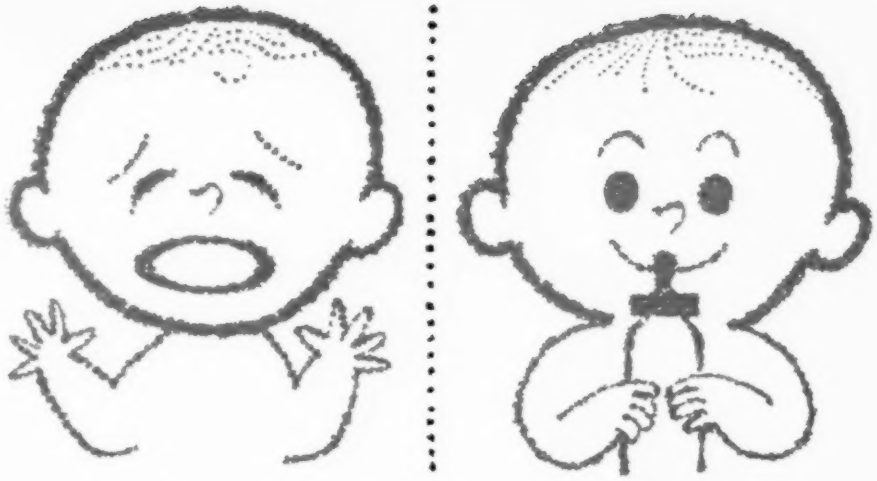
Protein	4.9%	Calcium	0.19
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.8

Calories per fl. oz., 32

*Made from Grade A Milk (U. S. Public Health Service Milk Code)

VARAMEL

THE BAKER LABORATORIES, INC.
Milk Products Exclusively for the Medical Profession
Main Office: Cleveland 3, Ohio • Plant: East Troy, Wisconsin



from whining to dining

NEW

BONADOXIN® DROPS

stop infantile colic.... *in hours*

.... *without barbiturates*

.... *without belladonna*

Each cc. BONADOXIN DROPS *contains:*

Meclizine Dihydrochloride 8.33 mg.

Pyridoxine Hydrochloride 16.67 mg.

BONADOXIN DROPS attack the known mechanisms of infantile colic with anticholinergic activity, tranquilizing effect, antihistamine action and prophylaxis against B_6 deficiency.

Dougan[1] reports the formula 88% effective in colic and pylorospasm. Litchfield[2] controlled most cases within 48 hours; *all* were controlled within 72 hours. No side effects were observed.[1,2]

1. Dougan, H. T.: An oral Therapy (Bonadoxin Drops) for infant colic and pylorospasm. Journal-Lancet *76*:135 (May) 1956. 2. Litchfield, H. R.: The use of meclizine dihydrochloride with pyridoxine in vomiting and pylorospasm in infants and children. In press.

ROERIG Chicago 11, Illinois

Dosage:

Age	cc.	Drops
Birth-3 mos.	0.5 to 1.5 cc.	15-45 daily
6 mos. to 2 yrs.	1.5 to 3.00 cc.	daily
2-6 yrs.	2.00-4.00 cc.	daily
older children	3.00-6.00 cc.	daily

PEACE of mind ATARAX®

Supplied in 30 cc. dropper bottles.

For all diarrheas regardless of etiology

CREMOMYCIN

SULFASUXIDINE®—NEOMYCIN SUSPENSION WITH KAOLIN AND PECTIN

When diarrhea brings misery to your patients, the prime consideration is prompt, lasting relief. CREMOMYCIN is so formulated that bacillary as well as nonspecific diarrheas respond promptly—often dramatically. The comprehensive, yet local antibacterial action of neomycin and Sulfasuxidine is concentrated in the gut and is complemented by kaolin and pectin, which soothe inflamed mucosa, adsorb toxins, and help normalize intestinal motility.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA

these are
the reasons for
Gantricillin

It provides Gantrisin® PLUS penicillin... for well-tolerated, wide-spectrum antibacterial therapy...in tablets of two strengths -- Gantricillin®-300 'Roche' for severe cases; Gantricillin (100) for mild cases -- and in an easy-to-take suspension for children -- Gantricillin (acetyl)-200.

Hoffmann - La Roche Inc . Nutley . N.J.

For troubles*

that are only

skin deep

(but very real to the patient)

TASHAN™

Cream

'Roche'

Stops itching...soothes...heals

*Eczema
Dry, scaly skin
Chafing
Diaper rash
Prickly heat
Pruritus ani, vulvae
Superficial ulcers
Contact dermatitis
Minor burns
Bedsores

Contains vitamins
A, D, E, and *d*-Panthenol
in a non-sensitizing
vanishing cream type base
which will please the
most fastidious patients.

ROCHE *Original Research in Medicine and Chemistry*

Medihaler

Means self-powered, uniform, measured-dose inhalation therapy...

Medihaler

Means true nebulization. Each measured dose provides 5 to 8 times as many particles in the ideal size range as most conventional nebulizers...

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate...

Medihaler

Means effective medications in an inert aerosol vehicle, in leakproof, spillproof, plastic-coated bottles...

Medihaler

Means utmost patient convenience—medication and Adapter together in plastic case, convenient for pocket or purse...

Medihaler

Means greater economy—no costly glass nebulizers to replace, and one inhalation usually suffices for prompt relief.

Medihaler®

THE UNIQUE MEASURED-DOSE INHALATION METHOD

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

Rx Medihaler-Epi™

Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Rx Medihaler-Iso™

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

Rx Medihaler Oral Adapter

Note: First prescription for Medihaler medications should include the desired medication and Medihaler Oral Adapter.

Oral Adapter made of hard plastic with no movable parts...foolproof...unbreakable and easily cared for by rapid rinsing...entire set, including medication, fits into neat plastic case small enough to be carried inconspicuously in pocket or purse...the smallest package for nebulization ever produced.

Notably safe and effective with children

Riker
LOS ANGELES

Designed FOR THE MOST DELICATE SKIN OF ALL...

DERMOLATE®

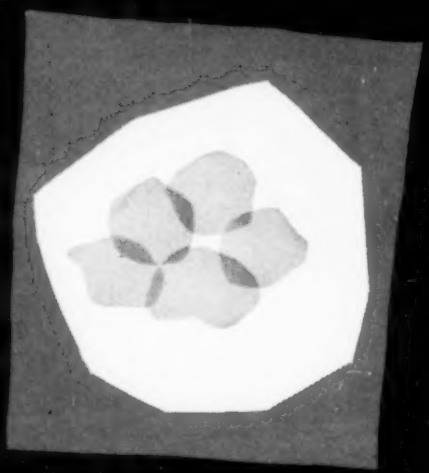
A remarkably mild, lathering skin detergent in cake form. It cleanses completely and is gentle for use on soap-irritable or acutely inflamed skin.
Dermolate is unsurpassed for routine daily bathing of infants and children.
...4 oz. cakes...

ACIDOLATE®

A bland, non-lathering cleanser in *liquid form*, that removes fat-soluble and water-soluble skin soil with equal efficiency. Acidolate is especially useful in pediatrics to dissolve oils and ointments on the skin and hair or for the removal of scales, crusts, "cradle cap" and vernix caseosa ...bottles of 8 fl. oz. and 1 gal....

WHITE LABORATORIES, INC., Kenilworth, N. J.

selected platelets make a select powder



bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

MYSTECLIN SUSPENSION

Steclin-Mycostatin (Squibb Tetracycline-Nystatin)

Another form of the only broad spectrum antibiotic preparation with added protection against monilial superinfection

PLEASANT TASTING — Mysteclin Suspension is pleasantly fruit-flavored and will appeal to taste-conscious youngsters as well as to adults who prefer liquid medication.

BROADLY EFFECTIVE — Mysteclin Suspension provides well tolerated therapy for the many common infections which respond to tetracycline—and also acts to prevent monilial overgrowth.

READY-TO-TAKE — Mysteclin Suspension requires no reconstitution and can be given by simple teaspoon dosage to patients of all ages.

MYSTECLIN SUSPENSION: a fruit-flavored oil suspension containing the equivalent of 125 mg. Steclin (Squibb Tetracycline) Hydrochloride and 125,000 units Mycostatin (Squibb Nystatin) per 5 cc. teaspoonful. Supplied in two-ounce bottles.

Also available as Capsules (250 mg. Steclin Hydrochloride and 250,000 units Mycostatin) and Half Strength Capsules (125 mg. Steclin Hydrochloride and 125,000 units Mycostatin).

SQUIBB *Squibb Quality — the Priceless Ingredient*

*MYSTECLIN®, *STECLIN®, AND *MYCOSTATIN® ARE SQUIBB TRADEMARKS

"... a highly effective antiemetic
and is safe for use in children."[1]

THORAZINE* *chlorpromazine, S.K.F.*

The safety and effectiveness of 'Thorazine' for control of vomiting in children has been confirmed by a number of clinicians.

Results in refractory cases have been particularly dramatic.[1-5]

'Thorazine' is available in ampuls, tablets and syrup, as the hydrochloride; and in suppositories, as the base.

Pediatric Bibliography

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*T.M. Reg. U.S. Pat. Off.

Smith, Kline & French Laboratories, Philadelphia

"your baby's doing fine...."

The physician trying to allay parental tensions and anxieties continually finds himself battling pressures of a competitive environment. At times even the most patient doctor may despair of the never-ending struggle.

To help tip the scales in the physician's favor, *Ross Laboratories have launched the Ross Developmental Series.*

The Series is designed to aid the physician in giving guidance and assurance. It can help to strengthen the bonds between physicians and parents, build healthy mother-infant relationship, motivate regular professional health supervision and counteract patient pressure. Available through your Ross representative or directly from Ross Laboratories, it includes wall charts, individual infant case records, a mothers' booklet, and folders on development.

ROSS DEVELOPMENTAL SERIES — Ross

SIMILAC®

for good infant nutrition

ROSS LABORATORIES, Columbus 16, Ohio

in diaper rash...

99% success reported for this means of therapy!

effective... A series of 500 cases of diaper dermatitis[1] was treated—with cure resulting in all but three infants. Wherever erythematous, intertriginous zones developed in the diaper region accompanied by the pungent odor of ammonia, treatment was instituted. Ammoniacal odor disappeared with gradual relief of symptoms. As a control, 50 healthy, normal infants were given prophylactic treatment. None developed ammonia dermatitis. PEDAMETH promises effective therapy!

safe... dl-Methionine is safe since it is actually one of the nutritionally essential amino acids. New and Non-Official Remedies (1952) states, "Because Methionine is low in toxicity, its use is not likely to be attended by any untoward effects". Goldstein[1] states that "untoward effects were conspicuously absent". PEDAMETH promises safe therapy!

convenient... Simply open a capsule and add the contents to the baby's daily formula, preferably while it is still warm. Or if preferred, it may be given in fruit juice or water. But no matter how it is given—PEDAMETH is convenient therapy!

1. Goldstein, Louis S., Clinical Medicine *59*:455 (1952).

Each capsule contains 0.2 Gm. of dl-Methionine.

prescribe

"PEDAMETH"
(dl-methionine

S·F·DURST & COMPANY, Inc., Philadelphia 20 Pa.

Send for samples and literature

they all grew up on

ABDEC® DROPS

CONCENTRATED MULTIVITAMIN SUPPLEMENT IN DROP FORM

PARKE, DAVIS & COMPANY • DETROIT, MICHIGAN

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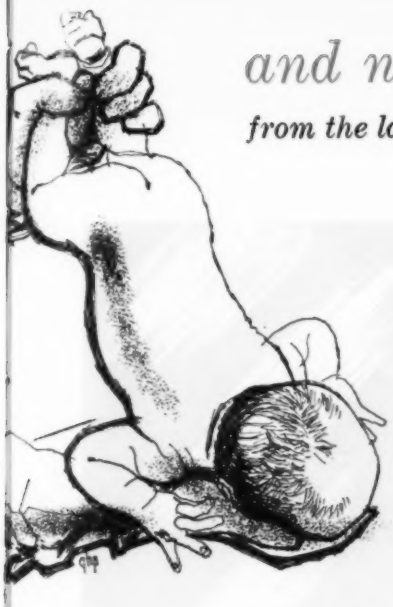


and now!

from the laboratories of Revlon Pharmacal:

MEDICATED
Baby Silicare Lotion

for the prevention of "Diaper Rash" and Dermatoses in infants

Medicated Baby Silicare Lotion has proved its efficacy in preventing cases of "diaper rash", intertrigo, napkin area erythema with mild papulo-vesicular eruptions, atopic eczema, contact dermatitis and bed sores.

In 577 cases* of newborns and infants up to eighteen months, Medicated Baby Silicare Lotion was used with excellent results. Through the many tests in institutions and at home it provided the desired protection and comfort in 96.5% of the cases under observation.

Medicated Baby Silicare Lotion is so gentle that it is used almost from the moment of birth as a cleansing and protective lotion. Mothers and nurses like its pleasant "feel"; it is cosmetically acceptable.

Since napkin dermatitis ("diaper rash") together with other types of dermatoses have been a problem to infants, mothers, and physicians for generations, Revlon developed Medicated Baby Silicare Lotion to thoroughly cleanse and protect the infant's skin. It is a prophylactic agent combining the moisture-repelling and bactericidal qualities so essential in prevention of dermatological conditions.

Baby Silicare is a combination of dimethylpolysiloxane (silicone) and hexachlorophene in an ethanolamine stearate lotion.

PHARMACAL DIVISION

745 Fifth Ave., New York, N.Y.

*Archives of Pediatrics 73:4 April 1956.

REVLON PHARMACAL DIV., DEPT. JP10
745 Fifth Ave., New York 22, N. Y.

Please send me a reprint of the article and a professional package of Medicated Baby Silicare Lotion.

Name_____

Address_____

City_____ Zone____ State_____

Unsurpassed Clinical Effectiveness

Desene Protective POWDER

for topical use in
TREATMENT and PREVENTION of

Chafing... DIAPER RASH... Prickly Heat

Noteworthy formulation, containing 15% *calcium undecylenate*, assures:

- **PROTECTION AGAINST IRRITANTS**
- **SAFE, PROLONGED BACTERIOSTATIC AND FUNGISTATIC ACTION**
- **FAVORABLE SKIN pH**

VIRTUALLY
NON-IRRITATING
AND
NON-SENSITIZING

Clinically tested at a well-known eastern foundling hospital, Desene cured 87% of rashes within 10 days. When used in prophylaxis, the incidence of rashes was 40% lower than in control series. Irritation was not observed even on excoriated skin.

Available at leading pharmacies
in 2 oz. shaker-top cans

Write for samples and literature

By the makers of
Desenex®

Maltbie
MALTBIE LABORATORIES DIVISION
WALLACE & TIERNAN INC.
25 MAIN ST., BELLEVILLE 9, NEW JERSEY, U.S.A.

PDS-3

IN THE TENSE, ANXIOUS CHILD . . . "THE CALMING EFFECT OF (ATARAX) WAS REMARKABLE"[1]

New ATARAX—the prompt, safe ataraxic—is now available in good-tasting syrup form for children.

CLINICAL REPORT. At the recent International Congress of Pediatrics, Bayart observed that "the calming effect of (ATARAX) was remarkable and allowed several of our little patients to attain distinctly more regular and more favorable scholastic results."[1]

Confirming other studies,[2,3,4] Bayart also found "the digestive and general tolerance was perfect."

FOR HYPEREMOTIVE CHILDREN. ATARAX imparts a calming effect without impairing mental alertness. Especially useful in hyperirritability, neuroses, nocturnal fears, tics of nervous origin. Dosage (for children over 3 years), usually two tsp. of ATARAX Syrup per day, or two 10 mg. ATARAX tablets, in divided doses. Supplied: Syrup in pint bottles, containing 10 mg. ATARAX per tsp. ATARAX tablets in tiny 10 mg. (orange) and 25 mg. (green) sizes, bottles of 100.

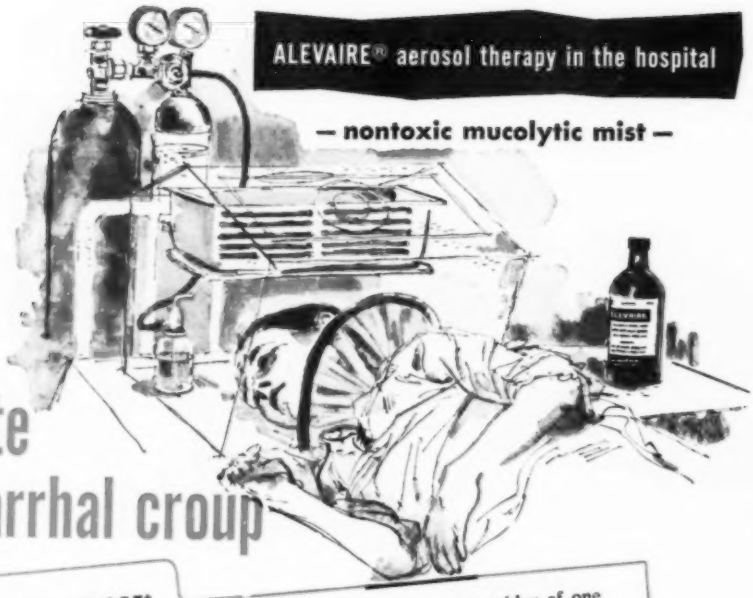
PEACE OF MIND ATARAX® SYRUP
(BRAND OF HYDROXYZINE)

1. Bayart, J.: On treatment by hydroxyzine of nervous conditions during childhood. Presented at the Int'l Congress of Pediatrics, Copenhagen, July 22-27, 1956. 2. Robinson, Harry M. et al: J.A.M.A. 161:604 (June 16) 1956. 3. Farah, L.: Int. Rec. of Med. and G. P. Clin. p. 379 (June) 1956. 4. Shalowitz, M.: Geriatrics 11:312 (July) 1956.

Roerig Chicago 11, Illinois

ALEVAIRE® aerosol therapy in the hospital

— nontoxic mucolytic mist —



acute catarrhal croup

CASE REPORT*

D D., a 2 year old male with fever, cough and laryngeal stridor of one day's duration, was hospitalized because of continued respiratory distress. Treatment had consisted of penicillin, injections and wet vapor inhalations.

Auscultation on arrival revealed harsh breath sounds on both sides and coarse rhonchi. Continuous crouping cough caused severe respiratory distress; the pharynx was injected and the tonsils were large. Diagnosis was acute catarrhal croup.

The child was placed in a croup tent with a humidifier, and antibiotics were administered. The condition did not change and Alevaire aerosol was begun in the evening. The cough gradually became easier and less frequent. The next day he rested comfortably, his temperature was reduced, no respiratory distress was noted, and the lungs were almost clear on auscultation. A day later no further therapy was required and the child was discharged on the fourth day after admission.

*Smessaert, Andre; Collins, V.J.; and Kracum, V.D.: *New York Jour. Med.*, 55:1587, June 1, 1955.

ALEVAIRE

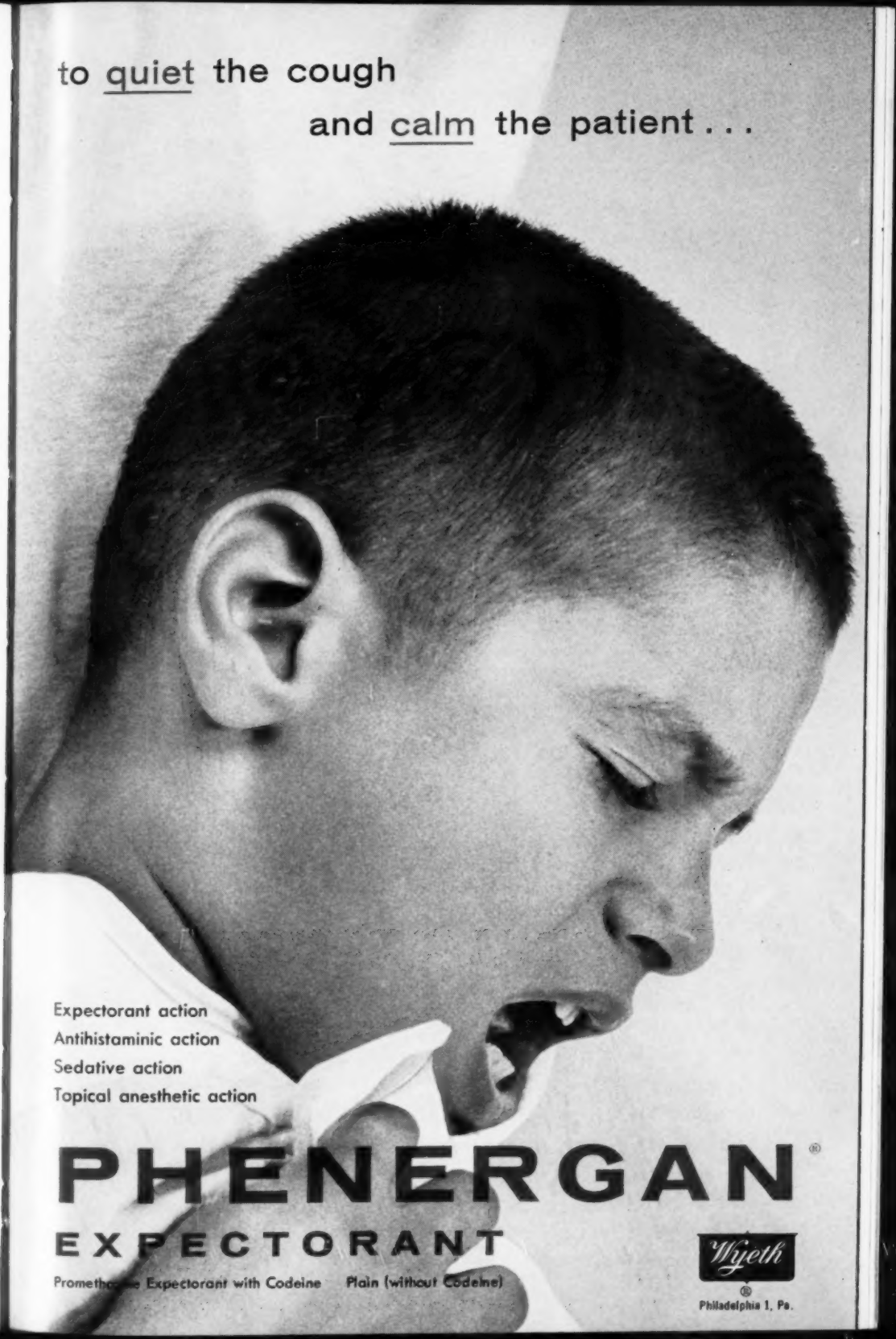
Alevaire is supplied in bottles of 60 cc. for intermittent therapy and in bottles of 500 cc. for continuous inhalation therapy.

Winthrop LABORATORIES
NEW YORK 18, N. Y. • WINDSOR, ONT.

Alevaire, trademark reg. U.S. Pat. Off.

has been dramatically effective in:

- neonatal asphyxia (due to inhalation of amniotic fluid, mucus obstruction, atelectasis)
- croup • laryngitis • tracheobronchitis
- pertussis • pneumonia • bronchial asthma
- emphysema • bronchiectasis • lung abscess
- pneumoconiosis • smoke, kerosene poisoning
- poliomyelitis (respiratory complications)
- routine oxygen therapy • tracheotomy
- prevention of postoperative pulmonary complications


to quiet the cough
and calm the patient . . .
Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action
PHENERGAN®
EXPECTORANT
Promethazine Expectorant with Codeine
Plain (without Codeine)
Wyeth®
Philadelphia 1, Pa.

Combined for a
on
resistant

new

METRETON *tablets*

METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

For prompt and effective relief, especially in many resistant allergic disorders, METRETON affords the benefits of two established agents with unexcelled anti-inflammatory, anti-allergic and antipruritic effectiveness. ***supported by essential vitamin C***—for stress support and for postulated effect on prolonging steroid action ***no better corticosteroid***—original brand of prednisone...minimal electrolyte effects—METICORTEN ***no better anti-histamine***—unexcelled in potency and freedom from side effects—CHLOR-TRIMETON effective against hay fever, pollen asthma, perennial rhinitis, acute and chronic urticaria, angioneurotic edema, drug reactions, inflammatory and allergic eye disorders, pruritic and contact dermatoses.

formula: Each tablet of METRETON provides 2.5 mg. of METICORTEN (prednisone), 2 mg. of CHLOR-TRIMETON maleate (chlorprophenpyridamine maleate), and 75 mg. ascorbic acid.

supplied: METRETON Tablets, bottles of 30 and 100.

frontal attack

allergies

new

METRETON *nasal spray*

METICORTELONE (PREDNISOLONE) PLUS CHLOR-TRIMETON

quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

Packaging: 15 cc. plastic "squeeze" bottle, box of 1.

METRETON,* brand of corticoid-antihistamine compound; METICORTEN,* brand of prednisone; METICORTELONE,® brand of prednisolone; CHLOR-TRIMETON,® brand of chlorprophenpyridamine preparations. *T.M.

MT-J-576

Schering

new tar-steroid therapy

for sub-acute

and chronic dermatoses

TARCORTIN*

CREAM

synergistic combination
effective in resistant
and refractory cases

Tarcortin contains coal tar extract and hydrocortisone, producing—

"A more rapid and more pronounced" clinical response than would be expected "from either medication alone."[1]

This synergistic effect brings prompt relief in atopic dermatitis, nummular eczema, dermatitis venenata, anogenital pruritus, seborrhea, and other chronic and resistant dermatoses . . . improvement is often noted within one week.

Recurrent episodes of various dermatoses "which became, eventually, refractory to hydrocortisone when used alone, occurred less frequently and did not become refractory to therapy" when the steroid was combined with an agent such as tar.[2]

1. Bleiberg, J.: Treatment of subacute and chronic dermatoses with a tar extract-hydrocortisone cream, J.M. Soc. New Jersey *53*: 371 (July) 1956.
2. Welsh, A.L., and Ede, M.: Hydrocortisone ointments: their rational use in dermatology, Ohio State M.J. *50*:837 (Sept.) 1954.

available: 7 gram and 1 ounce tubes.

formula: 0.5% hydrocortisone; 5% special coal tar extract (Tarbonis®)—greaseless, stainless hydrophilic vanishing cream base.

Apply twice daily to affected areas, and massage gently into skin until cream vanishes. No protective dressing is required.

R&C

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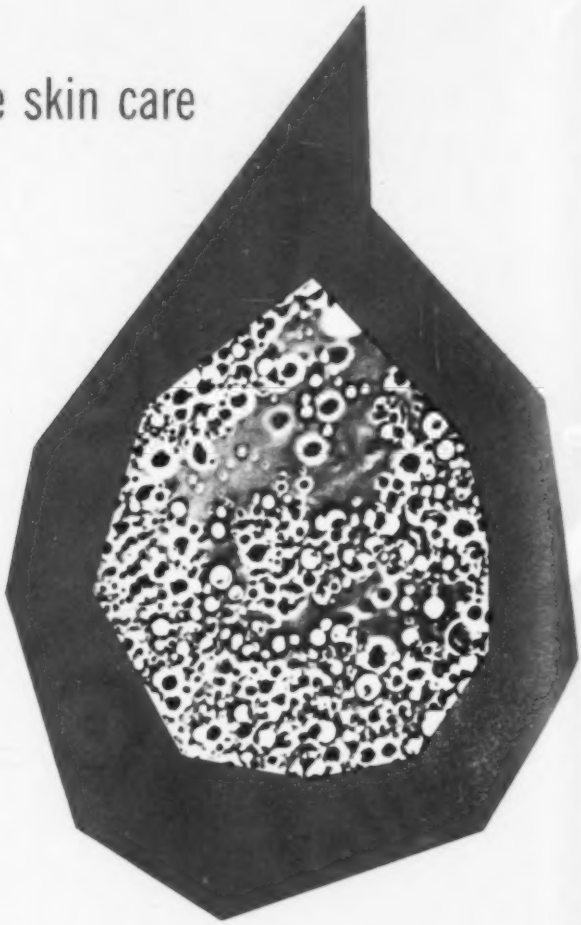
*Trademark and Pat. Appl.

a standard of excellence in pediatric care

Johnson & Johnson

PROOF

comprehensive skin care



Photomicrograph of Johnson's Baby Lotion. Discontinuous film of homogeneously dispersed, micron-sized oil droplets protects and lubricates skin—avoids occlusion.

due to discontinuous film plus antibacterial action

Johnson's

BABY LOTION

Johnson's Baby Lotion does more!
cleanses...lubricates...soothes and combats infections

Unlike many other lotions, Johnson's Baby Lotion forms a discontinuous protective oil film—not an impenetrable barrier. It is the only lotion containing hexachlorophene (0.5 per cent)—for potent, persistent bacteriostatic-bactericidal action. Routine use minimizes irritations—betters skin care.

nonirritating Johnson's Baby Lotion is a bland, nontoxic oil-in-water emulsion of specially compounded, pure mineral oil with lanolin. Has a neutral pH, is free from irritating hydrocarbons, contains no antioxidants or preservatives.

lets skin function normally Forms a meshwork of homogeneously dispersed, micron-sized oil droplets. This discontinuous film lets air reach the skin, permits normal heat radiation, allows perspiration to escape readily. Combats miliaria, other irritations.

combats infections Low surface tension of water-miscible lotion base permits antiseptic agent to mingle with skin moisture, come into close contact with the skin, rapidly control and terminate surface infections.

provides long-lasting protection Discontinuous film does not disappear readily—gives prolonged protection from irritants. Antiseptic gives long-lasting protection from common skin contaminants.

cleanses and lubricates thoroughly Water-miscible, removes foreign matter soluble in either oil or water. Optimal oil content gives excellent lubrication and spreads smoothly.

bettering baby care through specialized research

BABY PRODUCTS DIVISION

Johnson & Johnson

Report | from Carnation Research Laboratory

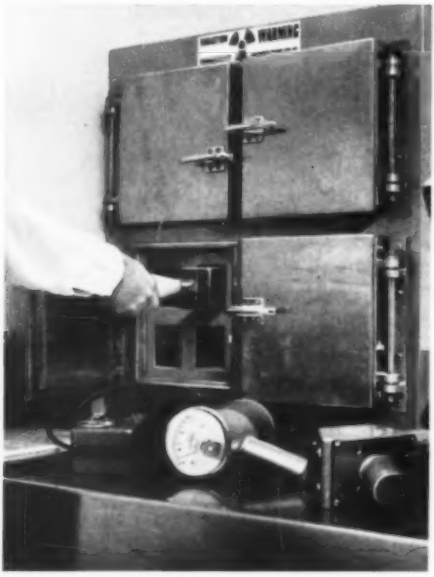
Van Nuys, California

5-Phase Research

For a half century, Carnation has conducted a continuous and expanding 5-phase research program in dairy and cereal products.

1. CARNATION FARMS

More than fifty years of scientific cattle breeding at Carnation Farms have resulted in many famous Holstein champions. Cattle from these famous bloodlines are shipped to dairy farms across the country to help improve the Carnation milk supply.



5. SPONSORED UNIVERSITY RESEARCH

Carnation sponsors University research in highly specialized fields, such as radiation and supersonic vibration, as related to dairy foods. Current projects are under way at the California and Massachusetts Institutes of Technology and the Universities of Wisconsin and Illinois.

2. CARNATION RESEARCH LABORATORY

Newest research facility is the Carnation Laboratory at Van Nuys, California, shown above – one of America's most modern laboratories devoted to product research. In addition to direct research in dairy and cereal foods, Carnation Laboratory coordinates the other phases of Carnation Research.

3. QUALITY CONTROL RESEARCH

Laboratories at each Carnation Plant exercise rigid day-by-day control of Carnation Milk processing. Samples from *all* Carnation plants are rechecked at Central Product Control, Oconomowoc, Wisconsin, to assure *uniform* high quality of Carnation Milk everywhere.

4. SPONSORED ASSOCIATION RESEARCH

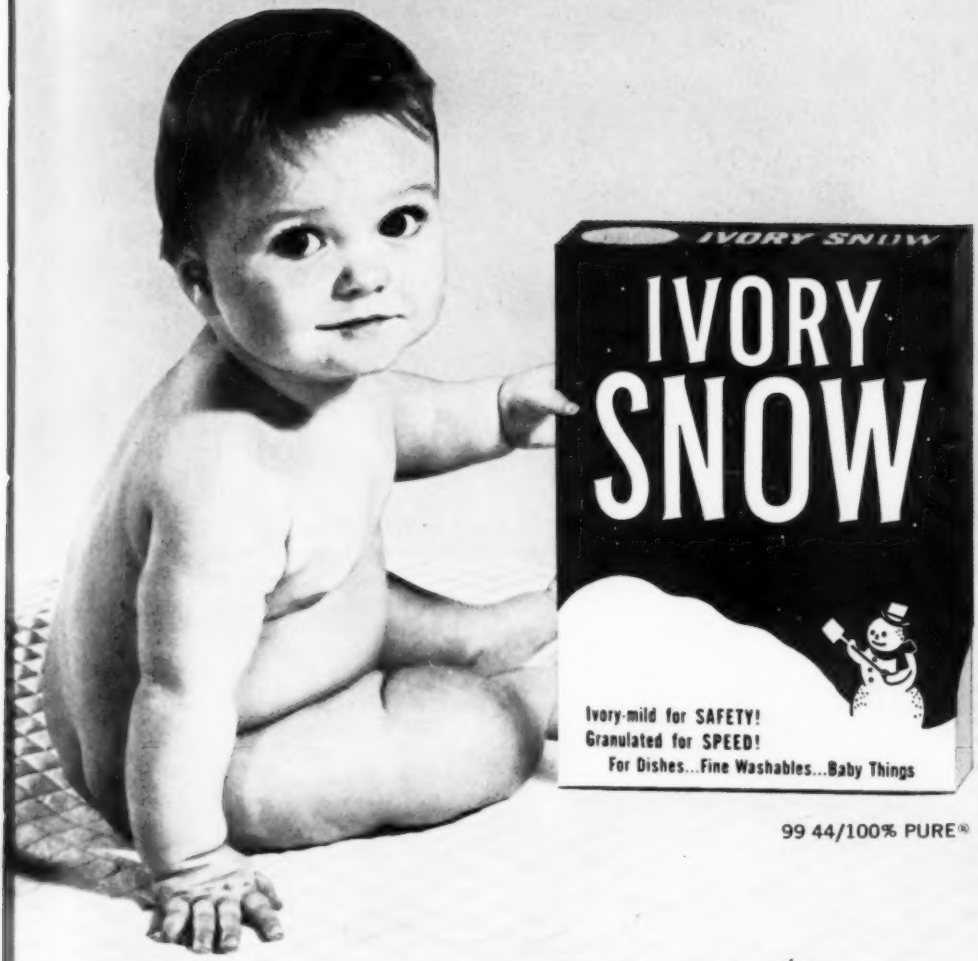
As a member of the National Research Council, Evaporated Milk Association, National Dairy Council, American Dry Milk Institute and many other similar organizations throughout the world, Carnation contributes importantly to the broad research activities conducted by these groups.

CARNATION PROTECTS YOUR RECOMMENDATION WITH CONTINUOUS 5-PHASE RESEARCH:

Carnation Farms,
Carnation Research Laboratory,
Carnation Plant Laboratories,
Carnation Central Product Control Laboratory,
Carnation-sponsored University and Association Research.

"from Contented Cows"

My Mommy washes all my things in Ivory Snow



99 44/100% PURE®

No wonder—because Ivory Snow is safe and mild as soap can be. It leaves diapers and baby clothes soft, smooth and free from irritating deposits that might chafe a baby's skin. And—since Ivory Snow is in the efficient granulated form preferred for washing-machine use—it's a practical soap for busy mothers with lots of baby wash to do.

A Procter & Gamble Product

BiB ACEROLA BERRIES
A tropical fruit . . . richest Natural-Food source of Vitamin C (average potency 1700 mg per 100cc), 50 to 100 times greater than oranges.*

A gift from Mother Nature

The discovery of BiB Acerola Berries opens broad new horizons for modern pediatric feeding. To determine acceptance for the infant dietary, a blend of Acerola and Apple Juice was subjected to controlled clinical studies . . . revealing these significant values:

Readily tolerated, even by children with allergic histories, BiB Apple-Acerola Juice may be introduced early into pediatric diets . . . a hypoallergenic, non-citrus source of Natural-Food Vitamin C.

Vitamin C in the blood plasma increases to "considerably above the average" pediatric levels, suggesting the possibility of greater utilization.*

Taste Acceptance is constant, assuring daily intake of Natural-Food Vitamin C (more than 40 mg per 100 cc in every can), plus the benefits derived from the supporting food nutrients.

Psychologically, the feeding ease is welcomed by mother and child, making juice-time a happy event.

BiB Apple-Acerola Juice is now available for your pediatric patients. Full size samples and the report on the clinical studies will be sent on request. Please write on your Rx blank or letterhead to: Medical Service, The BiB Corporation, Lakeland, Florida.

Only BiB packs 4 flavors to vary baby's diet . . . all scientifically-controlled for Natural-Food Vitamin C content, hypoallergenicity, flavor and feeding ease:

Orange Juice
Prune-Orange Juice
Apricot-Orange Juice
Apple-Acerola Juice

*Quoted from "Acerola Juice—Richest Known Source of Vitamin C" N. W. Clein, M.D., Journal of Pediatrics, 48:140 (Feb.) 1956

You May Prescribe BiB *With Confidence*

CHILDREN

VI-MAGNA*

SYRUP

Multivitamins Lederle

They just naturally go together!

Each teaspoonful (5 cc.) contains:

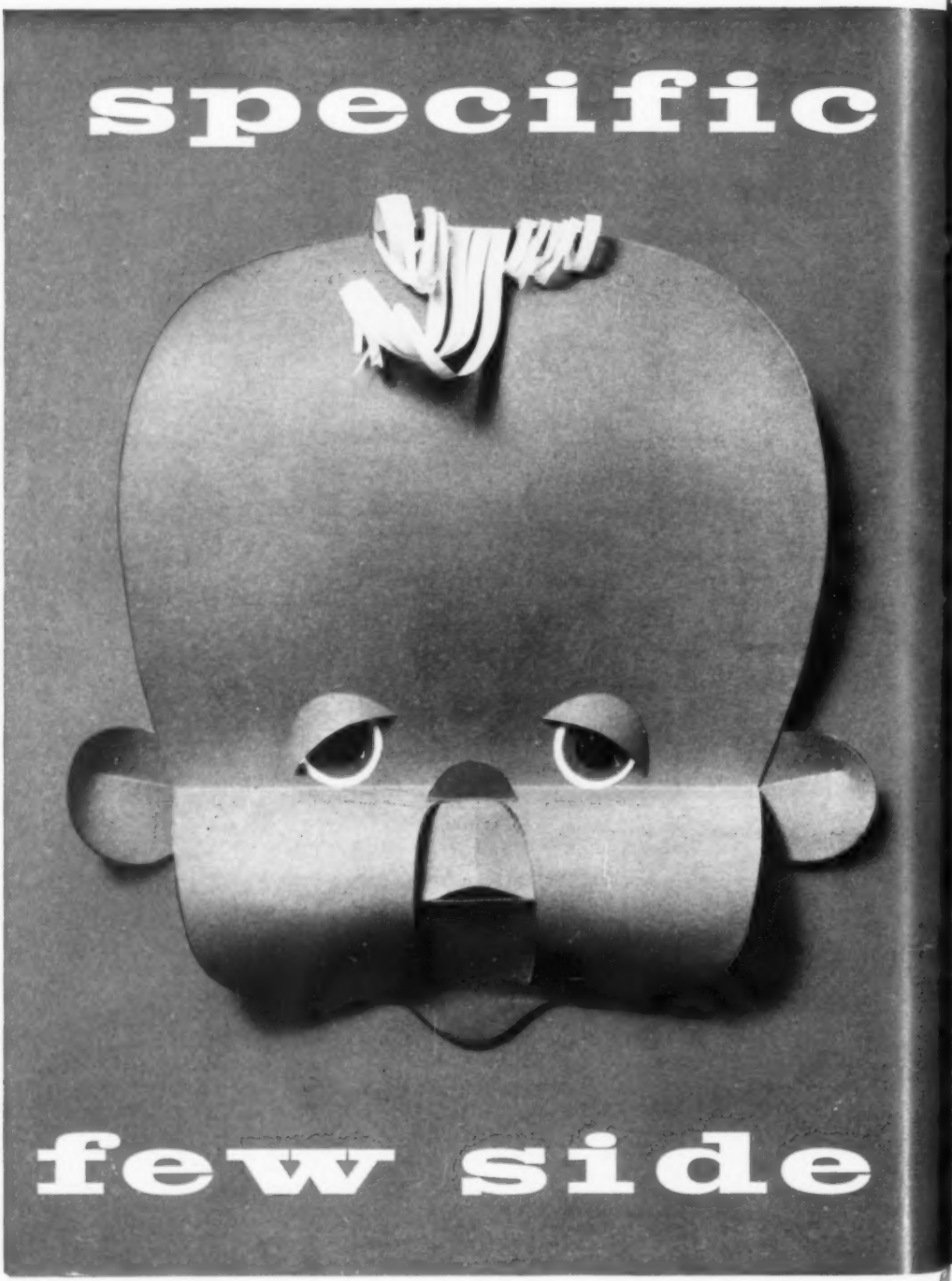
Vitamin A (Palmitate)	5000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Thiamine HCl (B_1)	3 mg.
Riboflavin (B_2)	2 mg.
Niacinamide	20 mg.
Ascorbic Acid (C)	75 mg.
Calcium Pantothenate	1 mg.
Pyridoxine HCl (B_6)	0.2 mg.
Vitamin B_{12}	5 mcgm.

A pleasant orange-lemon flavor makes VI-MAGNA Syrup tasty for any child. Each teaspoonful supplies nine essential vitamins, including vitamin B_{12}—and in quantities considerably greater than the minimum daily requirements for children. Because VI-MAGNA Syrup has no fishy taste or odor, it is readily taken as it comes from the bottle. Or it can be mixed in milk, infant's formula, fruit juice, or other liquid.

Lederle

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.


specific
few side

therapy

Specific—because you can actually pinpoint the therapy for coccic infections. That's because most bacterial respiratory infections are caused by staph-, strep- and pneumococci. And these are the very organisms most sensitive to ERYTHROCIN.

Pediatric

Erythrocin® STEARATE

(Erythromycin Stearate, Abbott)

ORAL SUSPENSION

Low toxicity—because ERYTHROCIN rarely alters intestinal flora. Thus, children seldom get gastroenteral side effects. Or loss of vitamin synthesis in the intestine. No allergic reactions, either. *Pediatric* ERYTHROCIN Stearate comes in a tasty, cinnamon-flavored suspension. In 75-cc. bottles Abbott

effects

THE OUTGROWN SHOE:

Enemy of children's feet

The outgrown shoe, for reasons which you know so well, has been called one of the greatest enemies of young feet by many authorities.

The makers of Buster Brown Shoes realize, as you do, that there is one way to combat this problem. And that is to get mothers to have their children's shoes *checked for size at regular, frequent intervals.*

An unfailing reminder

Therefore, the Brown Shoe Company has set up a system that enables Buster Brown retailers to make it easy, and automatic, for mothers to do just this. Every 90 days —regular as clockwork—each mother is sent a reminder that it's time to have her child's shoe size checked again.

And, to make certain that this important job is done right, the makers of Buster Brown Shoes conduct regular Fitting Clinics for retail salesmen.

Here, each salesman learns how to fit shoes by the approved Buster Brown 6-Point Fitting Method. This technique, which all Buster Brown retailers are pledged to use, eliminates guesswork and guards against the hazards of the ill-fitting shoe because . . .

1. Both feet are measured, and the longer foot size and greater width are fitted.
2. Big toe joint is fitted to the widest inside line of the shoe.
3. Small toe is fitted to the widest outside line of the shoe.
4. Adequate allowance is made from end of the toe to the end of the shoe.
5. Heel is fitted wide enough at bottom and snug enough at top.
6. The retailer reminds the mother every 90 days that it's time to have her child's shoe size checked again.

FREE EDUCATIONAL BOOKLET FOR GIVING TO PARENTS

To help you educate parents on how to care for their children's feet, we have prepared a factual, informative booklet called, "Parents' Guide to Healthy Feet for Children." It is available to you in quantity without cost. Simply mail this coupon.

Buster Brown Division
Brown Shoe Company
St. Louis 24, Missouri

Please send _____ copies of your new booklet.
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Address _____

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Buster Brown Shoes

AMERICA'S LARGEST SELLING CHILDREN'S SHOES

the first DATED Liquid Food Formula

S-M-A takes another step forward in infant nutrition. A unique *use-before* date, stamped in metal, is now on cans of S-M-A Concentrated Liquid. It assures your patient of always receiving a fresh can of liquid S-M-A.

Prescribe S-M-A for ease of preparation and for the full measure of benefits afforded by modern nutritional science.

SUPPLIED: S-M-A Concentrated Liquid, cans of 13.9 fl. oz. Also available: Instant S-M-A Powder, glass jars of 3.54 oz.; cans of 1 lb.

Comprehensive Formula for Sound Infant Nutrition

S-M-A®

Concentrated Liquid

Wyeth®

Philadelphia 1, Pa.

a new maximum
in therapeutic
effectiveness

a new maximum
in protection
against
resistance

a new maximum
in safety and
toleration

for
your
entire

multi-spectrum
synergistically
strengthened...

Sigma

CLEANDOMYCIN TETRACYCLINE

patient
population

a new certainty

in antibiotic therapy, particularly for the 90% of patients treated at home and in the office

Superior control of infectious diseases through superior control of the changing microbial population is now available in a new formulation of tetracycline, outstanding broad-spectrum antibiotic, with oleandomycin, Pfizer-discovered new antimicrobial agent which controls resistant strains. The synergistic combination now brings to antibiotic therapy: (1) a new fuller antimicrobial spectrum which includes even "resistant" staphylococci; (2) new superior protection against emergence of *new* resistant strains; (3) new superior safety and toleration.

mycin*

*TRADEMARK

Pfizer

Which child is being treated with old-fashioned nose drops? Which with 'VASOCORT'?

That's easy. The youngster on the right is being treated with 'Vasocort', the new concept of intranasal therapy.

Until the introduction of 'Vasocort', reduction of intranasal congestion and inflammation was usually achieved topically by vasoconstriction with potent pressor drugs—which all too often produce burning, stinging and rebound turgescence. These side effects are frequently even more unpleasant than the intranasal disorder itself.

'Vasocort', in contrast, owes much of its success in the treatment of children to its almost 100% lack of undesirable side effects. That is because of the extremely low concentrations of its anti-inflammatory agent (hydrocortisone) and of its *two* decongestants (phenylephrine and Paredrine*).

'Vasocort', which is rapidly replacing the traditional high-potency vasoconstrictor, has been administered over an extended period of time to children ranging from 9 months to 11 years. Results have been uniformly good.

VASOCORT*

(Hydrocortisone and 2 Decongestants)

Smith, Kline & French Laboratories, Philadelphia 1

*T.M. Reg. U.S. Pat. Off.

Formula—'Vasocort' is a stable, buffered, aqueous solution. It contains hydrocortisone alcohol, 0.02%; 'Paredrine' Hydrobromide (hydroxyamphetamine hydrobromide, S.K.F.), 0.5%; phenylephrine hydrochloride, 0.125%; preserved with thimerosal, 1:100,000.

EFFECTIVE TREATMENT . . .

White's Vitamin A and D Ointment soothes and encourages rapid healing of diaper rash as well as other raw surface lesions.

EXCELLENT PROPHYLACTIC ROUTINE . . .

White's Vitamin A and D Ointment after the infant's daily bath protects against diaper rash and other minor skin irritations.

AUGUST 25
DIAPER RASH

SEPTEMBER 1
NORMAL, HEALTHY SKIN

℞

White's

Vitamin A and D Ointment

WHITE LABORATORIES, INC., KENILWORTH, N. J.

KARO®... meets the need for a completely assimilable carbohydrate in infant feeding

Physicians and parents alike appreciate the efficacy, convenience and economy of Karo Syrup. For this double-rich, readily miscible mixture of dextrin, maltose and dextrose is easily digested, well tolerated and completely utilized.

Three generations of use as a milk modifier have shown that even premature babies thrive on Karo... and that its use does not induce flatulence, colic, fermentation or allergy.

Karo permits easy adjustment of formula and transition from liquid to solid food as circumstances demand. It may be used with sweet, acid, evaporated, dried or protein milk. Light or dark Karo each supply equivalent nutritive and digestive values... yielding 60 calories per tablespoonful.

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CORN PRODUCTS REFINING COMPANY
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LEDERPLEX LIQUID

. . . is a complete vitamin B-complex formula.

LEDERPLEX LIQUID

. . . is derived from pure beef liver.

LEDERPLEX LIQUID

. . . contains B_{12} and Folic Acid.

LEDERPLEX LIQUID

. . . always tastes good—palatable orange flavor

does not "wear thin" or go "flat"
over a prolonged dose regimen

LEDERPLEX* Vitamin B-Complex Liquid LEDERLE

Each teaspoonful (5 cc.) contains:

Thiamine HCl (B_1)	2 mg.	Pantothenic Acid	2 mg.
Riboflavin (B_2)	2 mg.	Choline	20 mg.
Niacinamide	10 mg.	Inositol	10 mg.
Folic Acid	0.2 mg.	Soluble Liver Fraction	470 mg.
Pyridoxine HCl (B_6)	0.2 mg.	Vitamin B_{12}	5 mcgm.

Also offered in Tablet, Capsule and Parenteral forms.

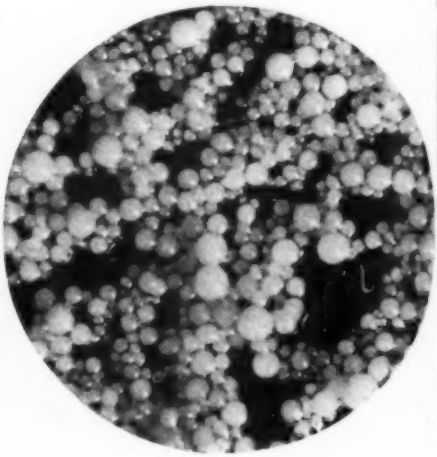
LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

Lederle

new "a pharmaceutical first"

Conventional Sulfa Suspension X 50



'SUL-SPANSION' X 50

The spheres shown here are but a few of the many thousands of micropellets in each spoonful of 'Sul-Spansion' liquid.

made only by Smith, Kline & French Laboratories, Philadelphia

first in sustained release oral medication

a safe, broad-spectrum antibacterial

in a new and unique sustained release

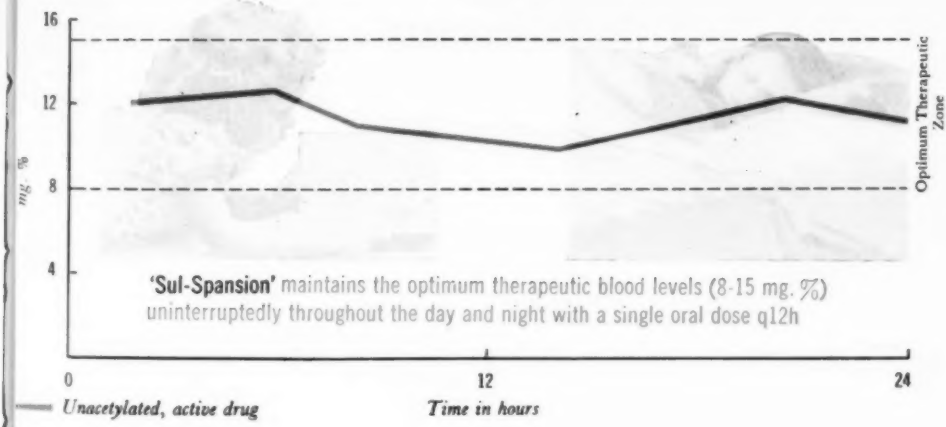
liquid form

Sul-Spansion*

sulfaethylthiadiazole, S.K.F.

(sulfa **Spansule*** suspension)
sustained release

especially for the common infectious states in children



'Sul-Spansion' maintains the optimum therapeutic blood levels (8-15 mg. %) uninterruptedly throughout the day and night with a single oral dose q12h

'Sul-Spansion' provides all these long-sought advantages in sulfonamide therapy:

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instantly restores normal acidity to the skin which has been made alkaline by contact with urine, and thus prevents diaper rash.
AVAILABLE: Creme in 4 oz. plastic jar, Lotion in 4 oz. plastic squeeze bottle.

CORT-DOME™ MICRONIZED HYDROCORTISONE
ALCOHOL in Exclusive Acid Mantle base, pH4.6.
AVAILABLE: Creme or Lotion, in ½, 1, 2 and 4 oz. sizes.

CRUDE COAL TAR—"The Most Valuable Local Remedy there is for Most Infants and Children with Atopic Dermatitis."*

KOLPIX®A and KOLPIX®D—Whole Crude Coal Tar in Exclusive Acid Mantle Base. "... the tar has been treated so that it is a medium gray color instead of black and the base is not greasy but water soluble. The strength of each is 2% tar. Kolpix 'A' is for acute, somewhat active eczema, Kolpix 'D' for chronic eruptions. Neither is very dirty. These are fine preparations – I use them a great deal."* AVAILABLE: 1 oz. tubes, 2 and 4 oz. jars.

*Lewis Webb Hill, M.D., "Treatment of Eczema in Infants and Children," Journal of Pediatrics, Vol. 47, No. 6, Dec. 1955.

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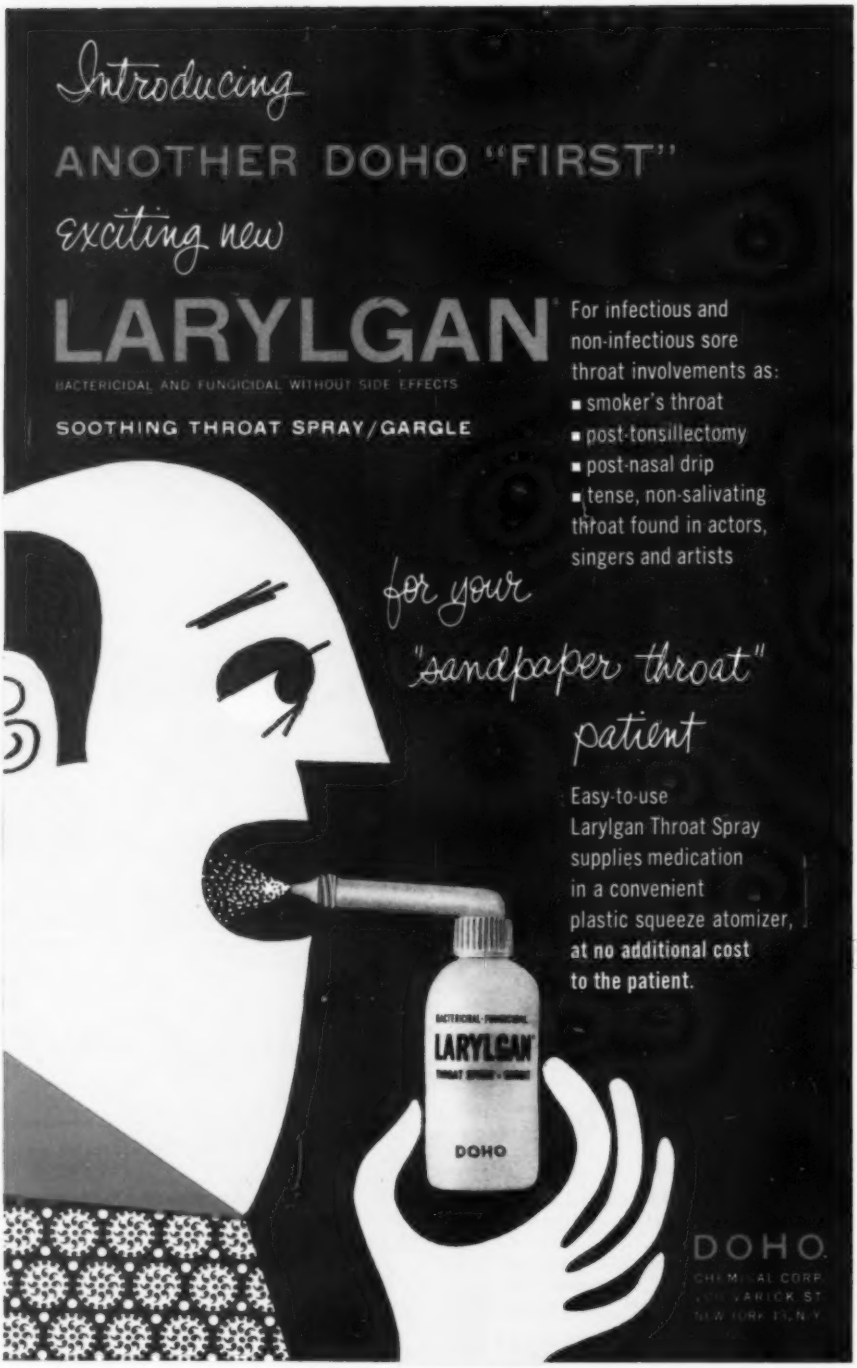
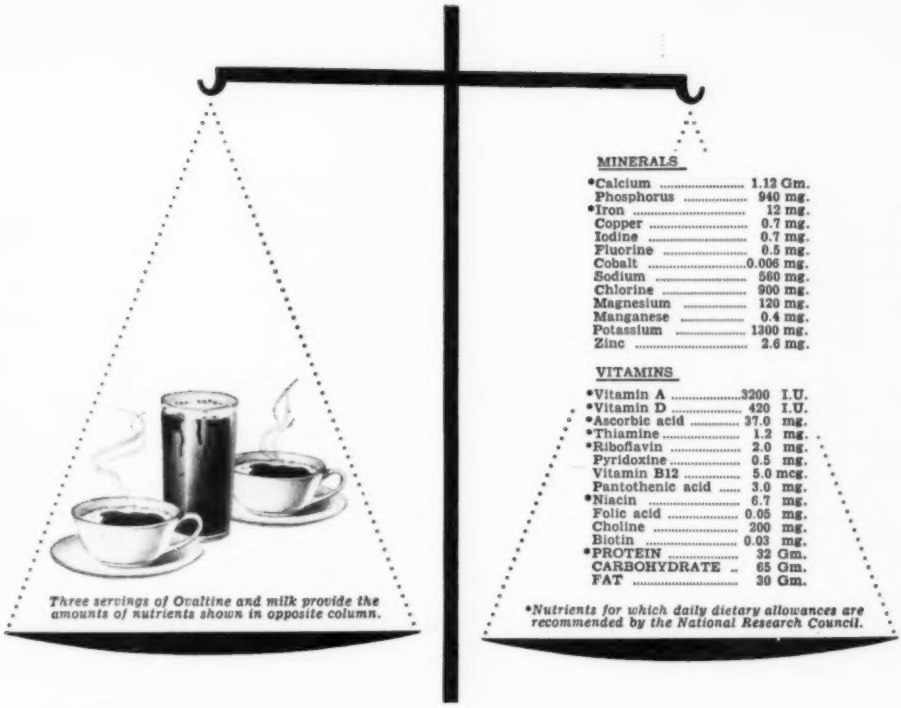


FORMULA: Anise Oil, 0.6%; Cassia Oil, 0.15%; Pine Oil, 0.2%; Menthol, 0.1%; Methyl Salicylate, 0.05%; Antipyrine, 0.28%; Pyrilamine maleate, 0.125%; Methyl Rosaniline Chloride (Crystal Violet), .002% in 2% Doho Glycerol; Ethyl Alcohol, 1.0%.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Folic acid ..... 0.05 mg.
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•PROTEIN ..... 32 Gm.
CARBOHYDRATE .. 65 Gm.
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Three servings of Ovaltine and milk provide the amounts of nutrients shown in opposite column.
•Nutrients for which daily dietary allowances are recommended by the National Research Council.

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AMMENS® gives soothing protection to babies' tender skin. And when diaper rash, prickly heat or other skin irritations make him restless, AMMENS eases discomfort, promotes healing.

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AMMENS is fluffy, white, and smells good, too. Tell baby's mother to keep a can of AMMENS handy.

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WHITE'S COD LIVER OIL CONCENTRATE CAPSULES—
12,500 Units of Vitamin A and 1250 Units of Vitamin D.

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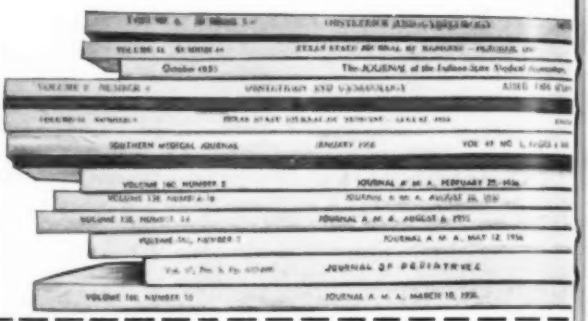
"...THE MOST EFFECTIVE HEMATINIC..."*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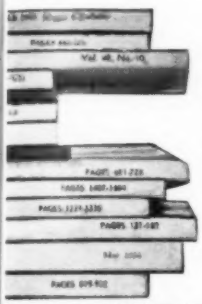

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*Ausman, D.C.: Cobalt-Iron Therapy in the Treatment of Some Common Anemias Seen in General Practice, the Journal Lancet (Oct.) 1956.

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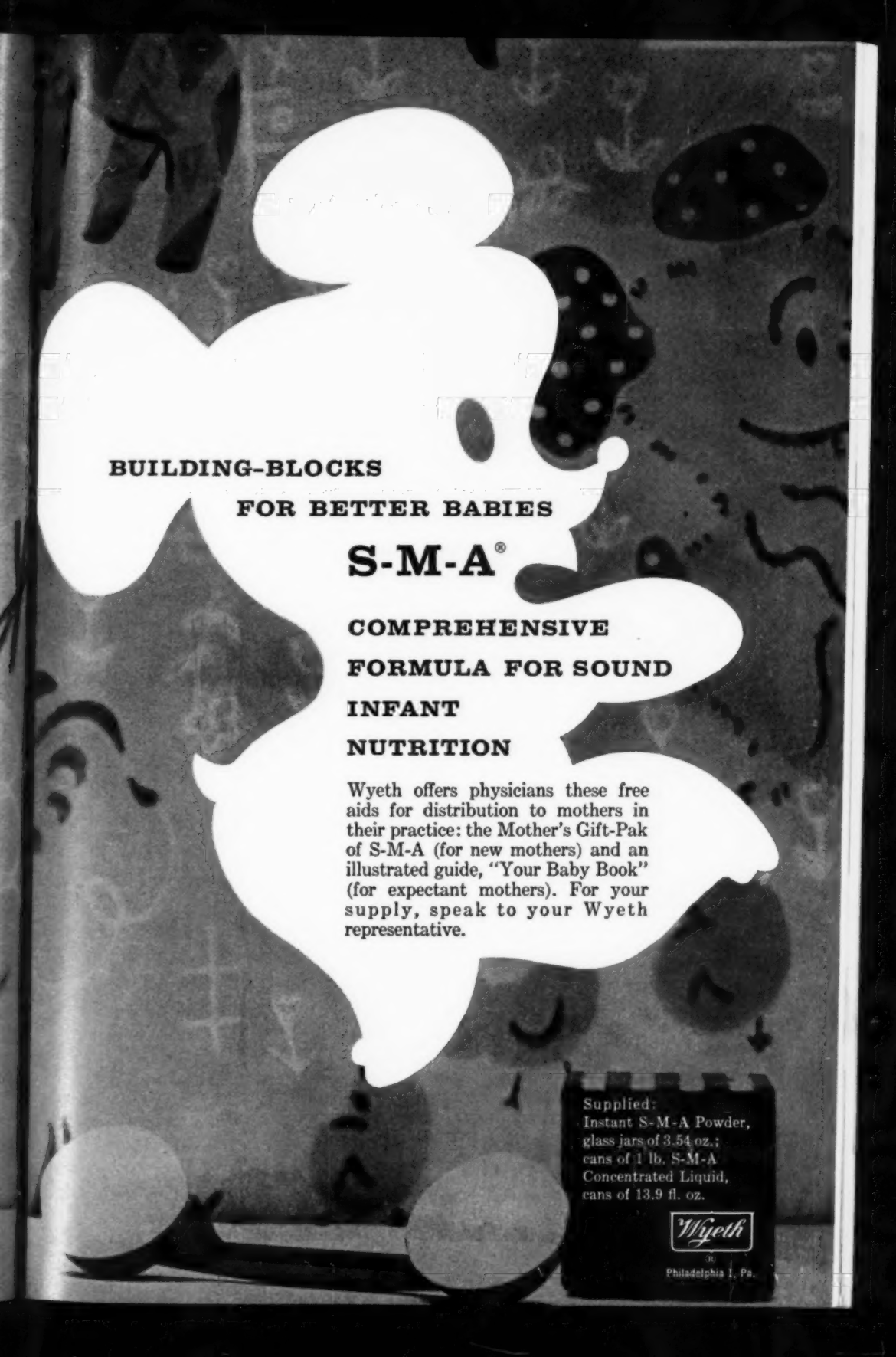
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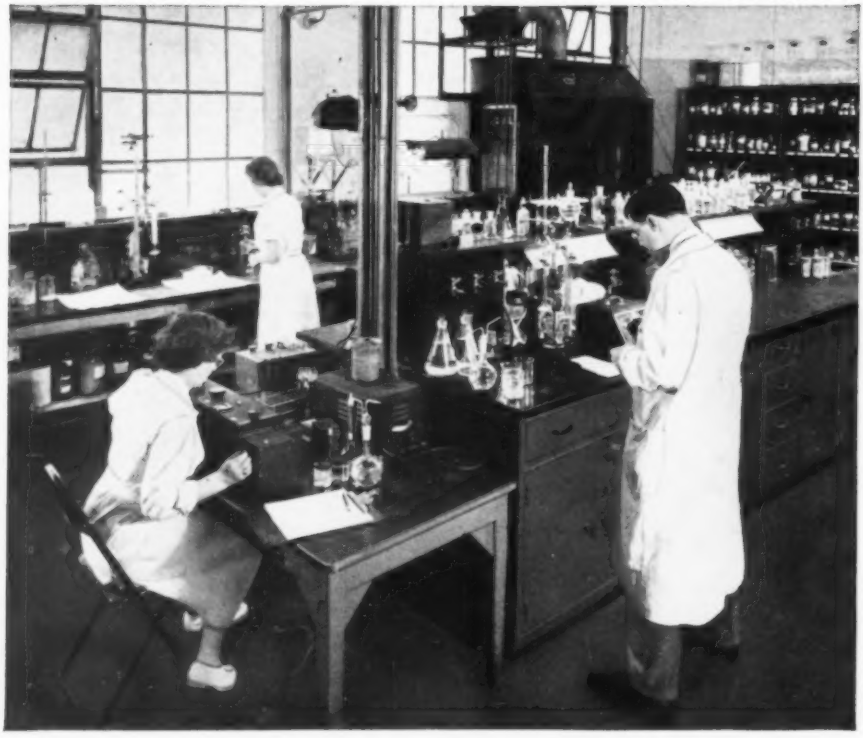

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Painstaking devotion to the highest standards of quality

This formula means buying only choice fruits and carefully cultivated vegetables from select farms and orchards. They are then painstakingly cleaned and prepared by Beech-Nut experts to preserve the "just picked" freshness and fine natural flavor, with maximum retention of vitamins and minerals.

5 Pre-Cooked Baby Cereals
28 Strained Foods
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TYLENOL*

...quick-acting pediatric antipyretic-analgesic

reduces fever,
relieves aches, pains:

Tylenol "produced effective antipyretic and analgesic responses..."[1]

without worry:

"no evidence of side-effects..." even on prolonged use[1]

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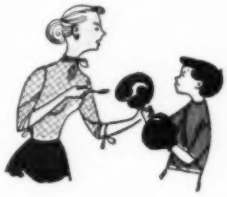

"Tylenol was considered 'acceptable' or 'liked' by... 86% of the children."[1]

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Elixir TYLENOL *for little "hot heads"*
(N-acetyl-p-aminophenol)

Bottles of 4 and 12 fl. oz.

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1. Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*:1219 (Apr. 7) 1956.

prevent iron deficiency anemia

Fer-In-Sol®

iron in a drop for infants and children

high pediatric incidence between 6 months and 2 years.[1] "Iron deficiency anemia has a peak incidence between six months and two and one-half years when a number of circumstances combine to deplete available stores."[2]

Fer-In-Sol maintains hemoglobin values at a constant level FER-IN-SOL in small daily doses is "... sufficient to maintain hemoglobin values at a constant level throughout the latter half of infancy in all full term infants."[3]

Fer-In-Sol supplies ferrous sulfate in an acidulous medium to enhance absorption and utilization. It is well tolerated, and its pleasant citrous flavor makes it readily acceptable to young children.

supplied: 15 cc. and economical 50 cc. bottles with unbreakable plastic "Safti-Dropper."

dosage: Prophylactic—0.3 to 0.6 cc. daily (0.3 cc. supplies 7.5 mg. of iron—more than the Recommended Daily Allowance for children up to 4 years old).
Therapeutic—1.2 to 2.4 cc. or more daily, in divided doses.

(1) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1:275, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30:155, 1954. (3) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86:553, 1954.

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LIQUID **Sobee**®
hypoallergenic soya formula | milk-free

a soybean protein food for sound nutrition

When you specify *Liquid* Sobee, the eczema and gastrointestinal disturbances caused by milk allergy are usually promptly relieved. These disturbances, when due to other food allergens, are also usually relieved by using *Liquid* Sobee as the basis of an elimination diet. *Liquid* Sobee is exceptionally well taken and well tolerated. Stools are satisfactory; diaper staining is no problem.

"Thermo-flash" sterilization gives *Liquid* Sobee a pleasant, bland flavor . . . attractive, light color . . . permits maximal preservation of amino acids and important B vitamins.

In a study reported by Kane,* babies on Sobee showed:
Satisfactory growth and nutrition . . . 99% relief of eczema, 90% relief of gastrointestinal and/or non-dermatologic symptoms . . . excellent acceptance.

*From an exhibit by Sydney H. Kane, M.D., at the American Medical Association meeting, Atlantic City, N. J., June 6-10, 1955.

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10 nutritionally significant vitamins

Assured stability including B_{12}

Delicious orange flavor

Easily administered teaspoon dosage

No refrigeration required

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it's easy to specify
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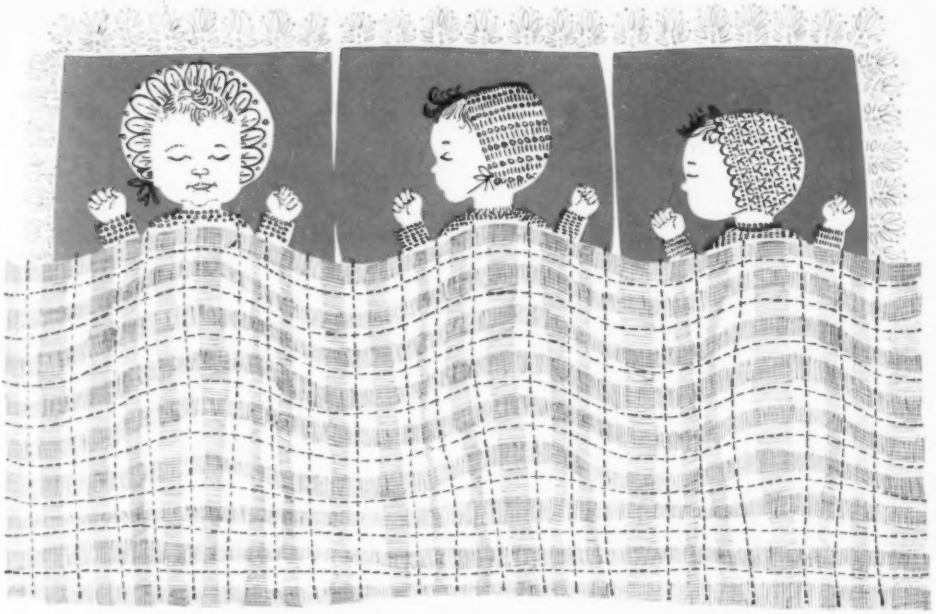

select the level of vitamin protection the baby needs for the critical first months

DECA-VI-SOL vitamins: A, D, C, B_1, B_2, niacinamide, biotin, pantothenic acid, B_6 and B_{12}

POLY-VI-SOL vitamins ...A, D, C, B_1, B_2 and niacinamide

TRI-VI-SOL vitamins...A, D, C

DECA-VI-SOL, POLY-VI-SOL AND TRI-VI-SOL

- highly stable—refrigeration not required
- readily accepted—exceptionally pleasant flavor, no unpleasant aftertaste
- full dosage assured—can be dropped directly into baby's mouth

In 15 cc., 30 cc., and economical 50 cc. bottles with the Mead calibrated, unbreakable plastic 'Safti-Dropper.'

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New...10 nutritionally significant vitamins including stable B_{12}

Poly-Vi-Sol®

6 essential vitamins

Tri-Vi-Sol®

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Swift takes pleasure, too, in helping baby enjoy that outstanding growth food, meat. Our recently developed process strains Meats for Babies the *smoothest ever*. Now these fine 100% meats are so tempting in texture—and in flavors, too—they help baby establish sound eating habits early in life.

You can recommend all 8 varieties of Swift's Meats, Egg Yolks and Egg Yolks & Bacon with confidence.

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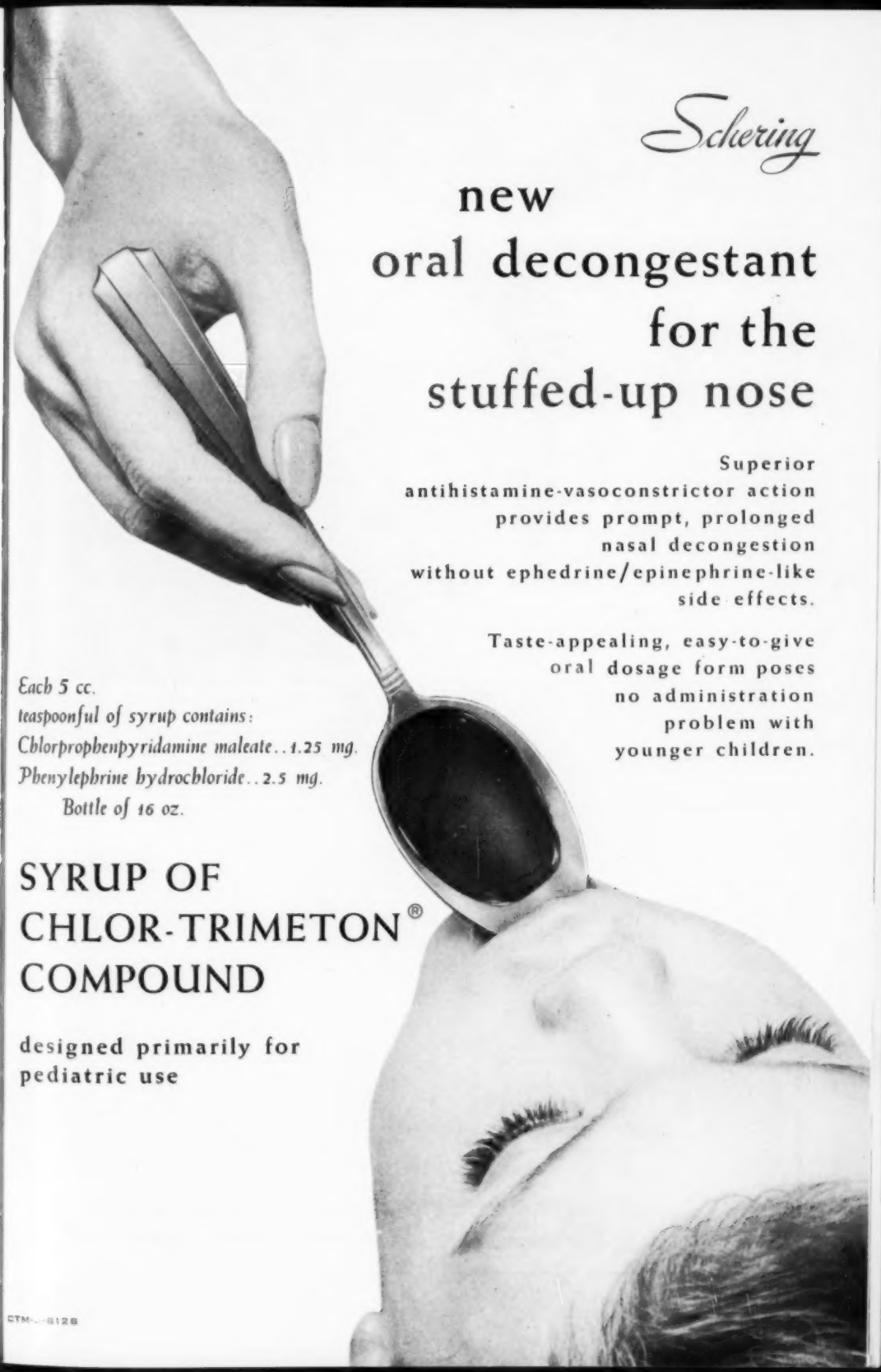

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new oral decongestant for the stuffed-up nose

Superior antihistamine-vasoconstrictor action provides prompt, prolonged nasal decongestion without ephedrine/epinephrine-like side effects.

Taste-appealing, easy-to-give oral dosage form poses no administration problem with younger children.

Each 5 cc. teaspoonful of syrup contains:
Chlorprophenpyridamine maleate..1.25 mg.
Phenylephrine hydrochloride..2.5 mg.
Bottle of 16 oz.

SYRUP OF CHLOR-TRIMETON® COMPOUND

designed primarily for pediatric use

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When weight-bearing starts...

the shoe of today shapes the foot of tomorrow

"When weight-bearing starts, the environment of the foot changes materially. It must be admitted that probably the most desirable course to follow would be to avoid shoes and to allow the child to go barefoot so that foot development could progress unhampered. This would certainly be so if the child's activities were carried out solely on springy turf or sandy beaches. Unfortunately, such conditions do not exist in modern life, as most of the child's weight-bearing is on hard and non-resilient surfaces which, lacking give and elasticity, put an additional strain on the growing foot from which *it must be protected by shoes.*"*

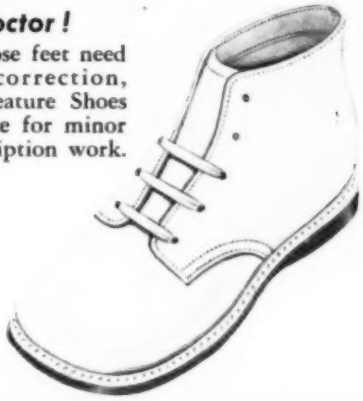
As the child's foot is soft bone which will not mature for many years, it may be easily bent and permanently damaged by poor fitting shoes. It is important, then, to carefully select shoes like CHILD LIFE. These shoes have a firm counter built into them to hold the heel in place. Ample room is provided for growing toes, and the sole is flexible for natural, unimpeded walking.

Child Life SHOES

are made in a complete line of sizes to meet the needs of children from infancy to adolescence. You'll find, too, that CHILD LIFE dealers have been selected for the time they will take to <u>*really fit*</u> the shoe to the child's foot. Names of dealers in your area will be gladly sent to you at your request.

. . . and Doctor!

for those children whose feet need additional help or correction, CHILD LIFE Arch Feature Shoes are especially adaptable for minor deficiencies and prescription work.



*Reference on request.

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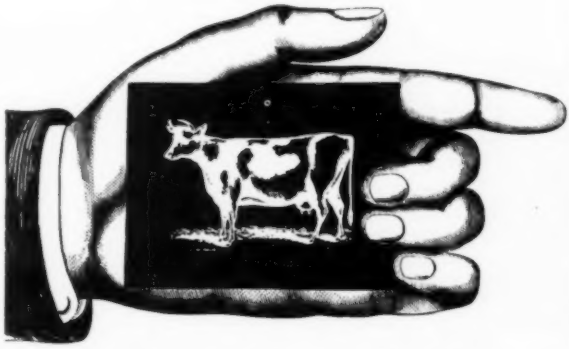
Milwaukee 45, Wisconsin

We've given the cow a hand!



HI-PRO Spray Dried Modified Cow's Milk takes up where cow's milk leaves off. It gives a 3-to-1 protein-to-fat ratio to patients in need of biologically complete protein content and low fat intake.

HI-PRO provides a full quota of calories without danger of fat irritation in cases of fat intolerance or where digestive disturbances are present. Readily digestible, it is ideal in treatment of infant diarrhea, prematures, fat intolerance and normal newborns.

infant diarrhea
Proteins are well-absorbed and supply calories lost by reduction in fat and carbohydrates.

prematures
Rapid growth plus low fat tolerance makes HI-PRO an ideal food.

fat intolerance
Protein is well-absorbed and caloric intake can be raised to any level without fat difficulties.

normal newborns
With HI-PRO, you can provide extra protein without fat for rapid growth and good tissue turgor.

hi-pro, analysis—dry

Protein	41%
Fat	14%
Carbohydrate	35%
Calcium	1.15%
Calories per oz.	121

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Pharmaceuticals, Inc.
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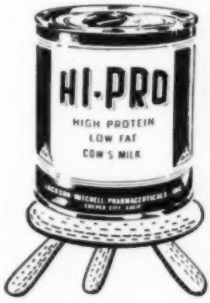
Serving the Medical Profession Since 1934



HI-PRO is available in 1-lb. and 2½-lb. vacuum-packed tins at all pharmacies.

Meat...

and the Child's Growth Tempo

Among the many factors affecting biologic growth, food adequate in quality and quantity to satisfy growth needs is basic for normal physical, mental, and social development in the child.[1]

Studies indicate that American children of the present generation are taller and heavier, on the average, than children of former generations.[2] Higher levels of nutrition are considered to be the most important responsible factor.

A wide spectrum of nutrients is essential for supporting good growth impetus in the child. Meat, an integral part of sound nutritional design, provides a pattern of amino acids highly effective in the biosynthesis of proteins utilized in tissue growth and renewal, in the fabrication of enzymes and hormones, in the regulation of the body's fluid balance, and in the production of antibodies. Omission of all good quality protein from the diet can seriously distort these body functions.[3] Meat, in addition, furnishes valuable amounts of B vitamins and minerals—iron, phosphorus, potassium, magnesium—which also serve fundamentally in physiologic processes concerned with normal growth and development.

---

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The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago... Members Throughout the United States

for "This Wormy World"

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'ANTEPAR'*

effective against

PINWORMS
and
ROUNDWORMS

'Antepar' is well-tolerated and pleasant to take.

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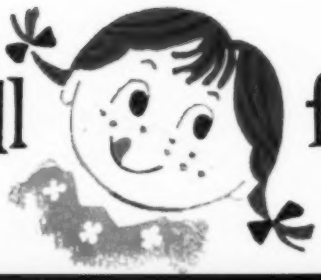
she's heard the call  for...

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And every mother should know that enriched bread is truly rich in many important nutrients, all of them needed for good nutrition, good nutritional health, and good growth: the vitamins thiamine, riboflavin, and niacin, the minerals calcium and iron, and good quality protein.

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1. Johnson, S. H., III, and Marshall, M., Jr.: A. M. A. Am. J. Dis. Child. 89:199, 1955.
2. Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. 54:805, 1955.

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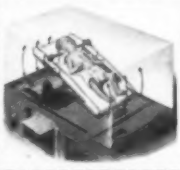

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break the reinfestation cycle rectally

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1. Allen, F. P., Jr.: J. Ped. 46: 155, 1955.

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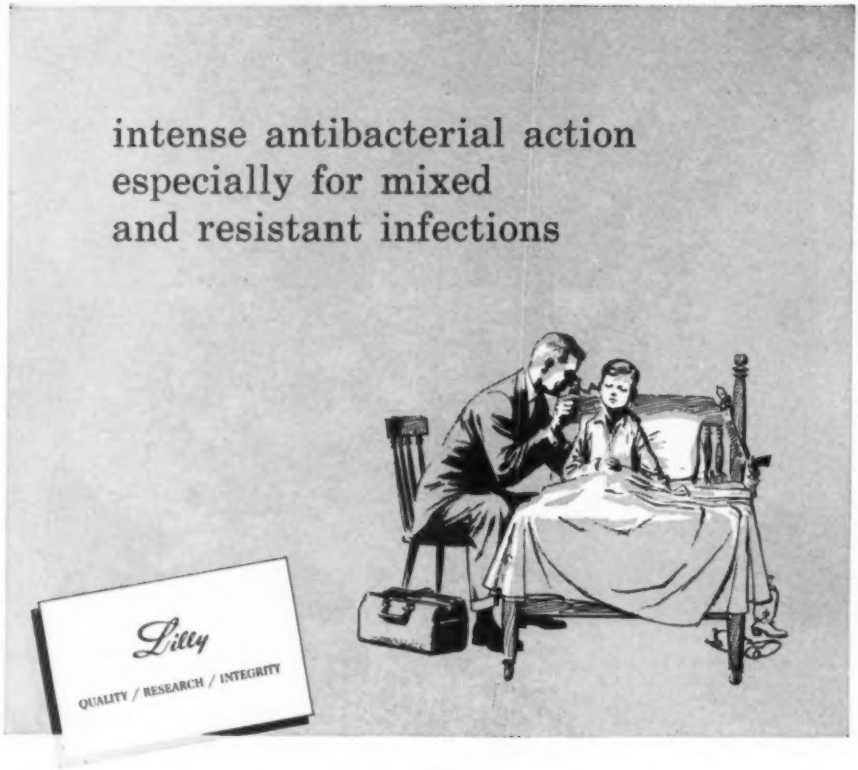

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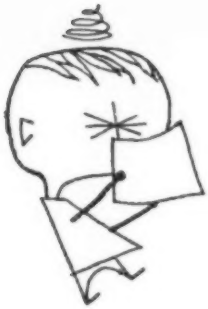

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1. Am. Heart J. **52**:300 (Aug.) 1956.
2. Ann. Int. Med. **40**:820 (Apr.) 1954.
3. Am. J. M. Sc. **227**:188 (Feb.) 1954
4. Ann. Int. Med. **39**:1189 (Dec.) 1953.
5. Am. Heart J. **45**:108 (Jan.) 1953.
6. Am. Heart J. **46**:276 (Aug.) 1953.
7. Arch. Int. Med. **90**:224 (Aug.) 1952.
8. Circulation **5**:201 (Feb.) 1952.
9. New Eng. J. Med.**246**:225 (Feb.) 1952.
10. Am. Heart J. **42**:292 (Feb.) 1951.
11. Fed. Proc. **9**:256 (Mar.) 1950.

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COMMON CONTAGIOUS DISEASES

By PHILIP MOEN STIMSON, A.B., M.D.

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and HORACE LOUIS HODES, A.B., M.D.

Pediatrician-in-Chief and Director of the Department of Pediatrics, Mt. Sinai Hospital; Clinical Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, New York City; etc.

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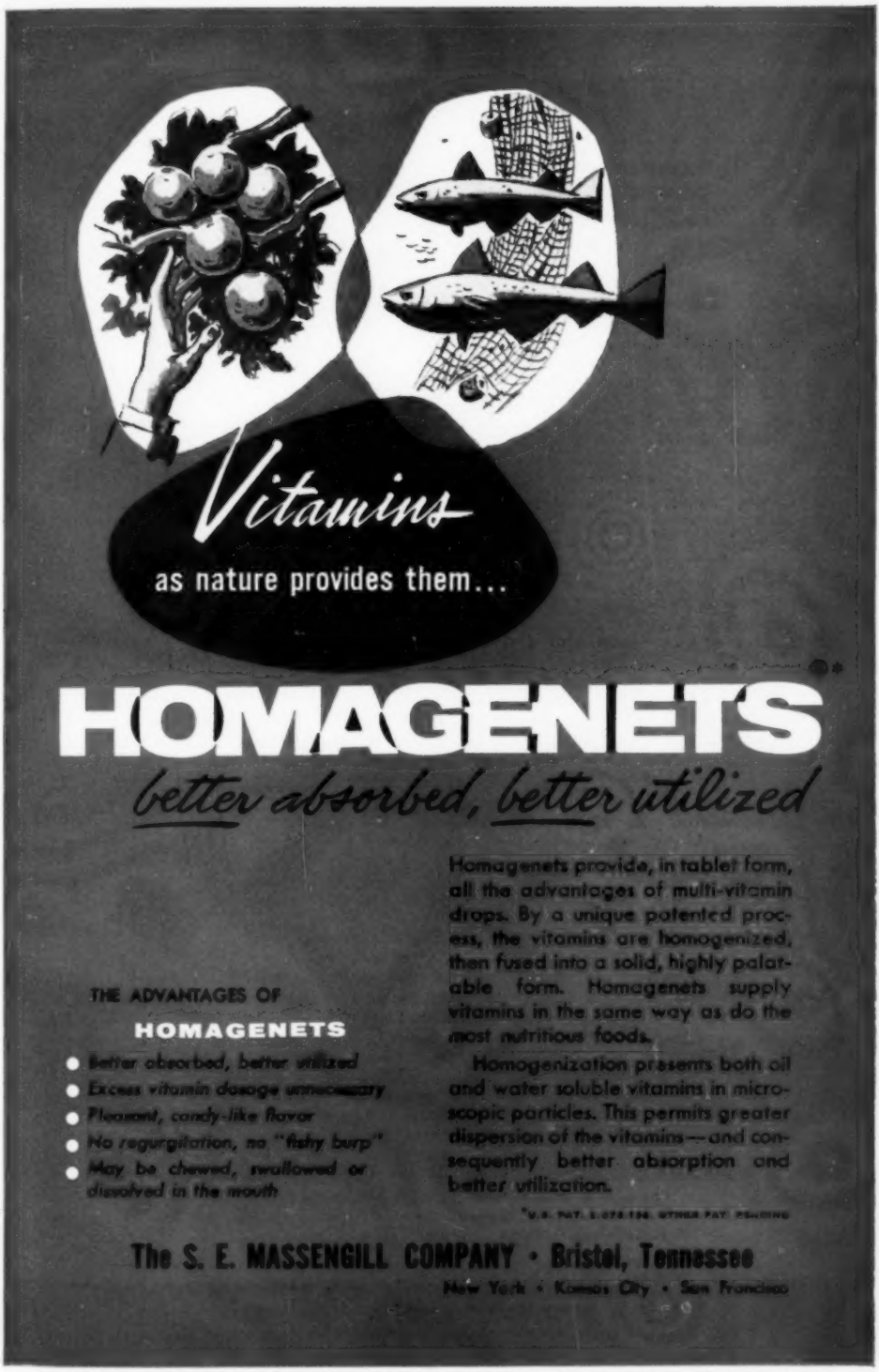
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MIGRAINE AND VASCULAR ALLERGY: Transactions of the Collegium Internationale Allergologicum, 2nd Symposium in Basel, 1955. Edited by R. R. A. Coombs, D. Harley and P. Kallos. 360 p., 136 fig., 1956 (Separatum vol. 7, nos. 4-6, and vol. 8, nos. 1-2 "International Archives of Allergy and Applied Immunology") US $9.50

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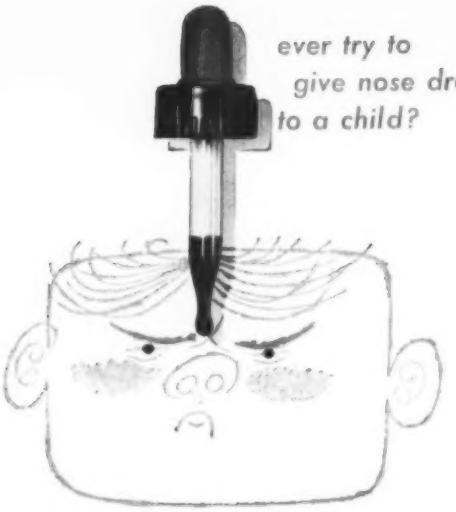

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Oral use of this synergistic combination of vasoconstrictor and antihistamine takes the furor out of decongestion...eliminates the risk of improperly used topical agents. Novahistine Elixir tastes good and is safe and easy-to-give. It causes no jitters or insomnia.

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Please send me—without charge—a supply of Novahistine® Elixir
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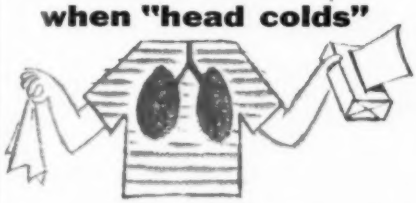
when "head colds"



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Fortified Novahistine with dihydrocodeinone for the control of coughs and respiratory congestion

Each teaspoonful (5 cc.) contains:	
Phenylephrine hydrochloride	10 mg.
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l-Menthol	1.0 mg.

(Alcohol content, 10%; sugar, 33⅓%)

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There's a difference:

Comparative composition of 100 gram portions: rennet-custards and commercially canned "Baby Desserts".

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*DESSERT A	94	2.0	2.7	20.2	76	63	Trace	0.111
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**RENNET-CUSTARDS (average of seven flavors)	96.5	3.2	3.6	12.7	123	102	175	0.164

*Nationally distributed "baby desserts" chosen.
**Made with fresh milk and "Junket" Rennet Powder.

Fresh milk is the basis of "Junket" rennet-custards. That is why they are higher in nutritional value than many commercially canned "Baby desserts". Rennet-custards furnish valuable protein, calcium and phosphorus needed for sturdy bone development and growth.

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"Junket" Rennet Tablets — not sweetened or flavored.

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for theoretical and practical information on
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Practical Pediatric Dermatology

by

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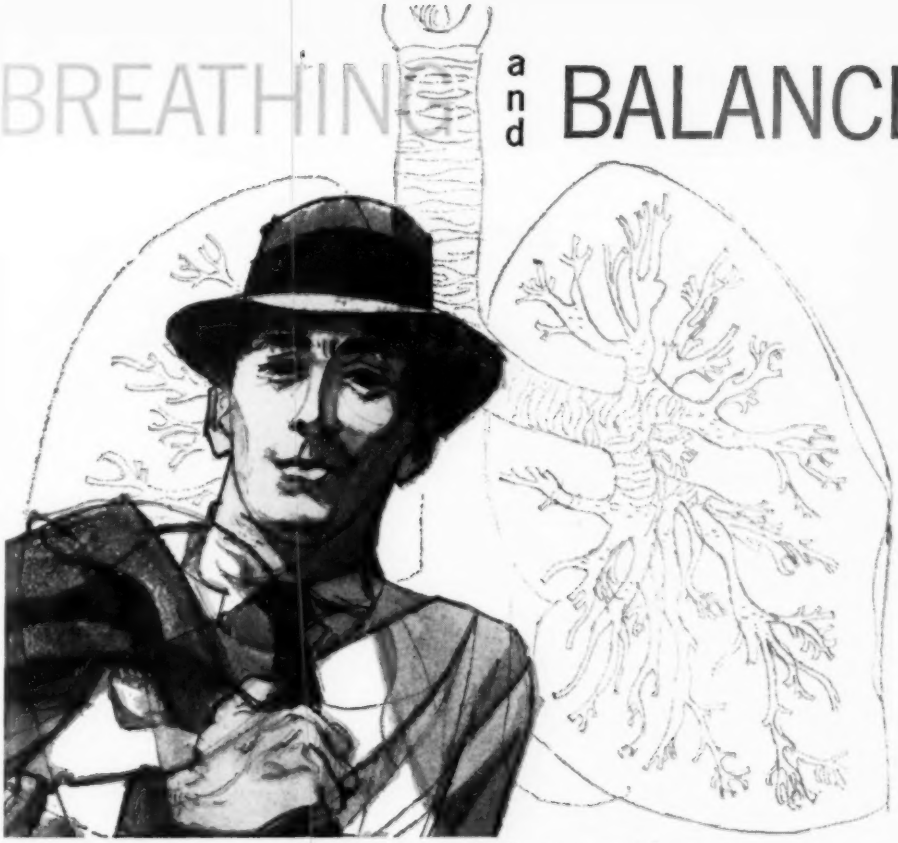

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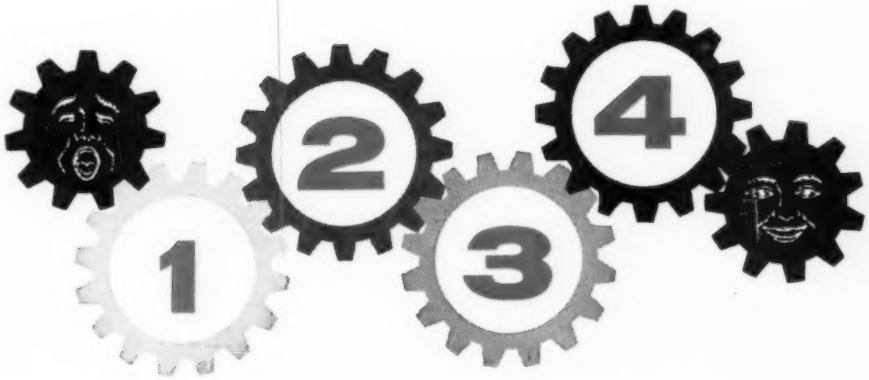

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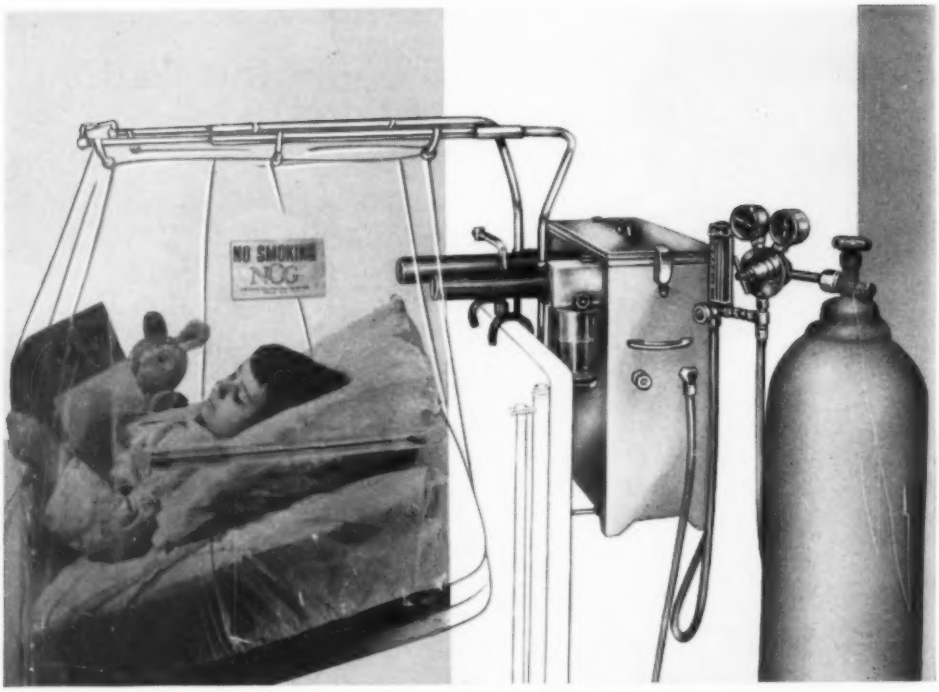

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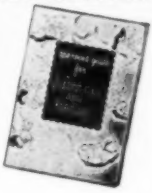

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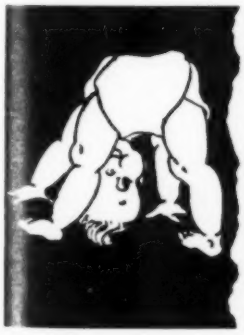

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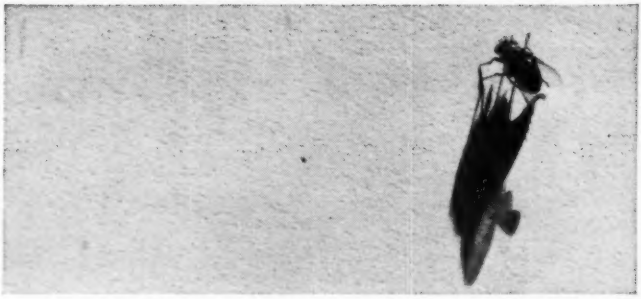

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